Applications of transition metal-catalysed coupling reactions in organic synthesis

Chapman, Christopher J.

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APPLICATIONS OF TRANSITION METAL-CATALYSED COUPLING REACTIONS IN ORGANIC SYNTHESIS

Submitted by Christopher J. Chapman

for the degree of PhD

of the University of Bath

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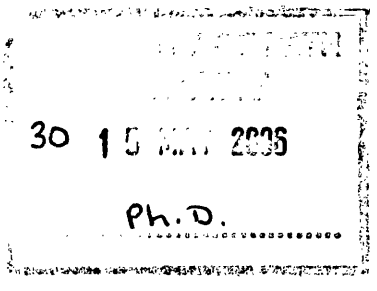
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Synopsis

Transition metal-catalysed transformations have become an integral tool in the synthesis of many biologically interesting and synthetically challenging molecules. Whilst the diversity of reactions catalysed and mediated by transition metals is vast, the activity within specific transformations is not solely a function of the metal. Indeed the ligands which bind to them often impart specific characteristics, which is particularly important when conducting enantioselective reactions.

This thesis describes the application of transition metal catalysts to synthetic organic reactions, focusing on the synthesis of amino acids and derivatives thereof.

The first chapter reviews the range of cross-coupling reactions involving organoboranes catalysed by palladium and rhodium, illustrating both recent methodological advances and topical applications of these reactions to synthetic challenges.

Chapter two describes the design and synthesis of novel hybrid phosphine-sulphone and phosphine-sulphonamide ligands with studies assessing the binding properties in transition metal complexes. Additionally primary catalytic results of these ligands in the palladium-catalysed Suzuki-Miyaura cross-coupling are presented.

The third chapter presents the efficient synthesis of unnatural amino acids *via* the rhodium-catalysed conjugate addition of boronic acids to dehydroalanine derivatives. Investigations into both the racemic and chiral additions are presented, together with further studies concerning the synthesis of chiral phosphine-based ligands.

Chapter four details primary research extending the methodology presented in chapter three to the synthesis of dipeptides.

Finally chapter five illustrates efforts to synthesis *N*-aryl-α-amino acids through two different catalytic methods using rhodium and palladium.

Acknowledgements

I would like to thank my supervisor Dr. Chris Frost for all his enthusiasm, ideas, advice and encouragement throughout the duration of my PhD and undergraduate studies; and for humouring some of my designs for ligands.

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Contents

Abbreviations

Å	angstrom(s)
Ac	acetyl
acac	acetyl
Ala	alanine
anhyd	anhydrous
Anal.	analytical (spectrometry)
app.	apparent
aq	aqueous
Ar	aryl
9-BBN	9-borabicyclo[3.3.1]nonyl
9-BBN-H	9-borabicyclo[3.3.1]nonane
Bn	benzyl
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
$B_{mim}PF_6$	1-butyl-3-methylimidazolium hexafluorophosphate
Boc	*tert*-butoxycarbonyl
$(Boc)_2O$	*tert*-butylpyrocarbonate
br	broad (spectral)
Bu	normal (primary) butyl
t-Bu	*tert*-butyl
Bz	benzoyl
°C	degrees Celsius
calcd	calculated
cat.	catalytic quantity
Cbz	benzyloxycarbonyl
CDAP	1-cyano-4-dimethylaminopyridium tetrafluoroborate
cm^{-1}	wavenumber(s)
COD	1,5-cyclooctadiene
COE	cyclooctene
CuTC	copper(I) thiophene-2-carboxylate
Cy	cyclohexyl
δ	chemical shift in parts per million downfield from tetramethylsilane

d	day(s); doublet (spectral)
dba	dibenzylideneacetone
DCC	*N,N'*-dicyclohexylcarbodiimide
DCM	dichloromethane
°	degrees (angle)
DIEA	di*iso*propylethylamine
DMA	dimethylacetamide
DMAP	4-(*N,N*-dimethylamino)pyridine
dmba	*N,N*-dimethylbenzylamine
DME	1,2-dimethoxyethane
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
dppb	1,4-bis(diphenylphosphino)butane
dppe	1,2-bis(diphenylphosphino)ethane
dppf	1,1'-bis(diphenylphosphino)ferrocene
dppp	1,3-bis(diphenylphosphino)propane
EDCI	*N*-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide hydrochloride
EI	electron impact (in mass spectrometry)
Et	ethyl
equiv.	equivalent(s)
FAB	fast atom bombardment (in mass spectrometry)
g	gram(s)
h	hour(s)
H-BCat	catecholborane
HMPT	hexamethylphosphorustriamide
HOBT	1-hydroxybenzotriazole
HPLC	high-performance mass spectrometry
Hz	hertz
IR	infrared
J	coupling constant (in NMR spectrometry)
L	liter(s)
Leu	leucine
Lys	lysine

ν	wavenumber(s)
LHMDS	lithium hexamethyldisilazane, lithium bis(trimethylsilyl)-amide
lit.	literature
μ	micro
μW	microwave
m	milli; multiplet (spectral)
M	molar (moles per liter); mega
M^+	parent molecular ion (in mass spectrometry)
Me	methyl
MHz	megahertz
min	minute(s)
mol	mole(s)
MOM	methoxymethyl
mp	melting point
MS	mass spectrometry
MVK	methyl vinyl ketone
m/z	mass-to-charge ratio (in mass spectrometry)
nap	naphthalene
NMR	nuclear magnetic resonance
Ph	phenyl
Phe	phenylalanine
ppm	part(s) per million
Pr	propyl
i-Pr	iso-propyl
q	quartet (spectral)
qu	quintet (spectral)
R_f	retension factor (in chromatography)
rt	room temperature
s	singlet (spectral)
SDS	sodium dodecyl sulfate
Sep	septet (spectral)
t	triplet (spectral)
TEBA	benzyltriethylammonium chloride

TFA	trifluoroacetic acid
TFP	tri-2-furylphosphine
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMS	trimethylsilyl; tetramethylsilane
t_R	retention time (in chromatography)
trt	triphenylmethyl (trityl)
Ts	*p*-toluenesulfonyl (tosyl)
Tyr	tyrosine

CHAPTER ONE:

Organoboranes in Transition Metal-Catalysed Organic Transformations

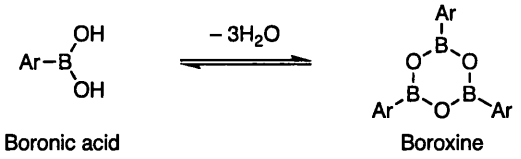
1 Organoboranes in Transition Metal-Catalysed Organic Transformations

1.1 INTRODUCTION

The carbon-carbon (C-C) bond lies at the very heart of organic chemistry, and our ability to synthesise innovative and interesting organic molecules is inextricably linked to the discovery of new techniques that form these bonds. Recent years have seen the continued increase in the application of transition metal catalysts as a means for C-C bond formation. The dominance of these reactions is demonstrated by the number of processes concerning palladium which share the names of those who discovered them. These include the Mirozoki-Heck,[1] Stille[2] and Suzuki-Miyaura[3,4] reactions which permit the cross-coupling of substrates previously unimaginable.[5] Increasingly these reactions are becoming the basis for the successful and efficient synthesis of complex organic molecules.

Many of the original transition metal-catalysed reactions made use of reagents which are, or form products that are toxic, or difficult to handle under ambient conditions; such as stannanes, Grignards, and lead reagents. In contrast, however, boronic acids and their derivatives are often crystalline solids, stable to air and moisture. Organoboron compounds are highly electrophilic, however, the organic groups display mild nucleophilicity, thus limiting the use of organoboron reagents in ionic reactions, akin to Grignard reactions. Fortunately, organoboron reagents are sufficiently reactive for transmetallation to other metals to occur, in the presence of a suitable base.

Although a large number of boronic acids and their derivative are commercially available, novel organoboron reagents can be prepared by a number of routes[3,4,6] including: boronation of organometallics such as organolithium or magnesium reagents, hydroboration of alkenes and alkynes and transition metal-catalysed B-C coupling. It should be noted that most boronic acids readily undergo dehydration to form the cyclic trimeric anhydride (boroxine; 1,3,5,2,4,6-trioxatriborinane) (Scheme 1), often occurring spontaneously at room temperature the separation of the free acid from the anhydride is therefore often difficult. However, since in most cases the acid or the anhydride will undergo the required reaction, they can usually be regarded as equivalent.



Scheme 1

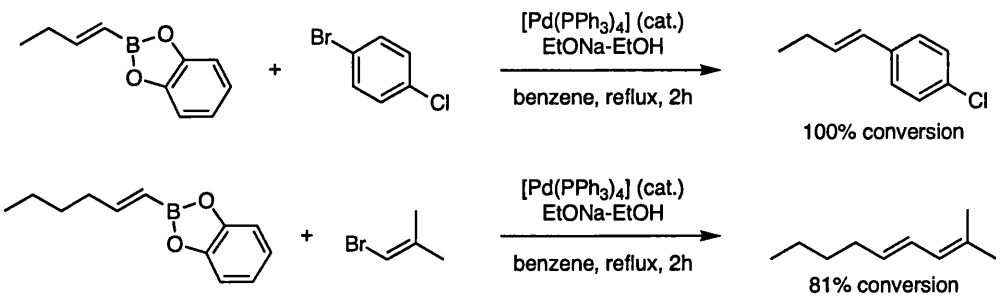
This review shall focus on bi-molecular cross-coupling reactions of boronic acids catalysed by palladium and rhodium, thus those reactions involving three or more components (i.e. the carbonylation reaction or the homo-coupling reaction) shall not be covered. Although this review cannot be exhaustive, it is the intention to illustrate the current efforts of organometallic chemists in this area, focusing specifically on work reported in the past few years. This review is organised by the transition-metal employed (palladium, rhodium). It is noteworthy that this classification is also historically consistent for the main procedures covered, those of the Suzuki-Miyaura and 1,4-conjugate addition reactions.

1.2 PALLADIUM-CATALYSED CROSS-COUPLING REACTIONS OF ORGANOBORON COMPOUNDS

1.2.1 The Suzuki-Miyaura Reaction

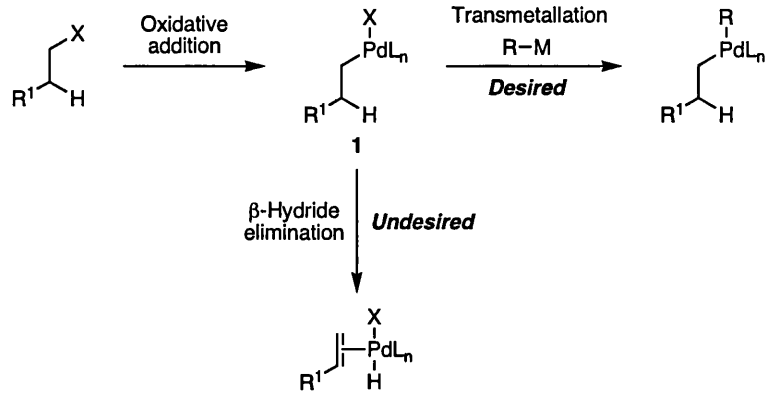
A Brief History

Miyaura and Suzuki first published the palladium-catalysed cross-coupling of alkenyl boranes with alkenyl-, alkynyl-, and aryl-halides in 1979 with two concurrent publications.[7] The desired coupled products were generated in high yields when the reactions were performed in a basic toluene solution heated to reflux (Scheme 2).



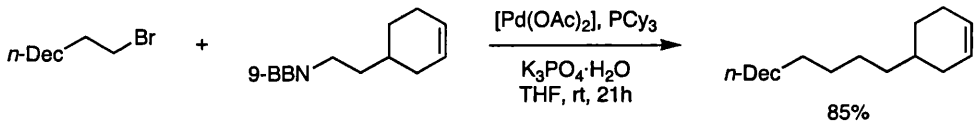
Scheme 2 Foundation work by Miyaura and Suzuki

Numerous research groups have since studied and extended these early results, producing an extensive number of publications on what is now possibly the most widely studied of the palladium-catalysed reactions. The methodology has been modified to enable the coupling of the aryl-, vinyl- and alkylboronic acids and related boronates. Fu and co-workers have recently reported the efficient coupling of alkyl halides at room temperature;[8,9] previous attempts at the coupling of alkylhalides failed, resulting in the formation of an alkene (corresponding to the alkylhalide) *via* β-hydride elimination from the palladium alkyl complex **1** (Scheme 3).



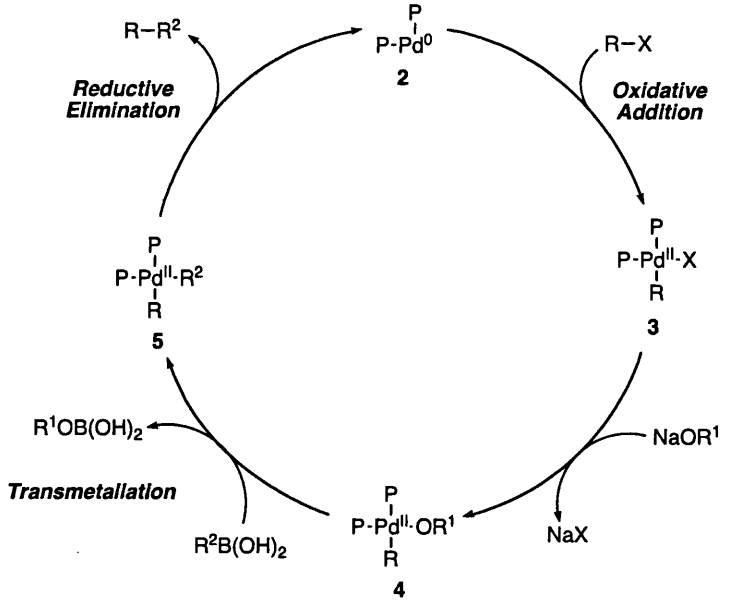
Scheme 3

$[Pd(OAc)_2]/PCy_3$ in the presence of $K_3PO_4 \cdot H_2O$ serves as an efficient catalyst for the alkyl-alkyl coupling (Scheme 4). Interestingly, PCy_3 displays unique activity in the reaction conditions, with arylphosphines, and other electron rich trialkylphosphines ineffective ligands for this transformation.[9] However, these conditions were optimal only for the Suzuki cross-coupling of alkyl bromides with 9-BBN derived reagents. Later work reported by Fu, cited the use of the commercially available ligand P(*t*-Bu)$_2$Me with $[Pd(OAc)_2]$ as an efficient catalyst in *tert*-amyl alcohol, as solvent, with KO*t*-Bu as base.[8] The use of P(*t*-Bu)$_2$Me as ligand afforded the coupled product from the reaction of 1-bromooctane with phenylboronic acid in 85% isolated yield compared to 63% for PCy_3.



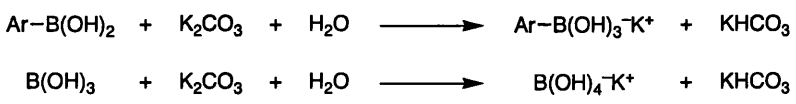
Scheme 4

The generally accepted mechanism for the Suzuki-Miyaura cross coupling is presented in Scheme 5. Oxidative addition of the organohalide to the palladium (0) complex followed by ligand exchange, through the addition of base, gives the Pd(II)alkoxide complex **4**. Subsequent transmetallation of the alkoxide with the organoborane affords complex **5**, with the final step being the reductive elimination of the coupled product and concomitant regeneration of the catalytically active Pd(0) species **2**.



Scheme 5 Proposed mechanism for the Suzuki-Miyaura

However, Smith *et al.* have presented findings, which indicate the need for a basic solution (pH >9). Under these conditions phenylboronic acid is transformed into trihydroxyphenyl borate ($PhB(OH)_3^-$), which the authors suppose is the active species allowing direct transmetallation with the palladium halide complex. Kinetic studies indicated the need for water and base to activate the boronic acid, and it was thus assumed that one mole of water and base was required to initially activate the boronic acid and then to neutralise the resulting boric acid (Scheme 6).[10]

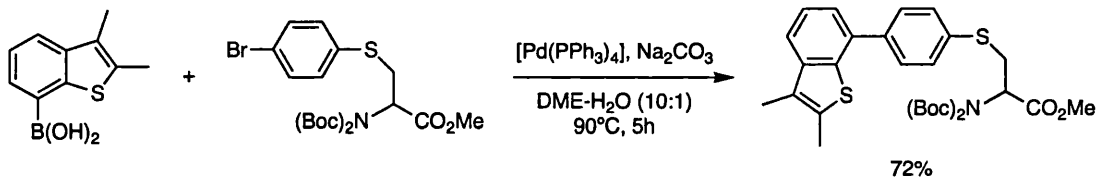


Scheme 6

Applications of the Suzuki-Miyaura cross-coupling to the synthesis of unnatural Amino Acids

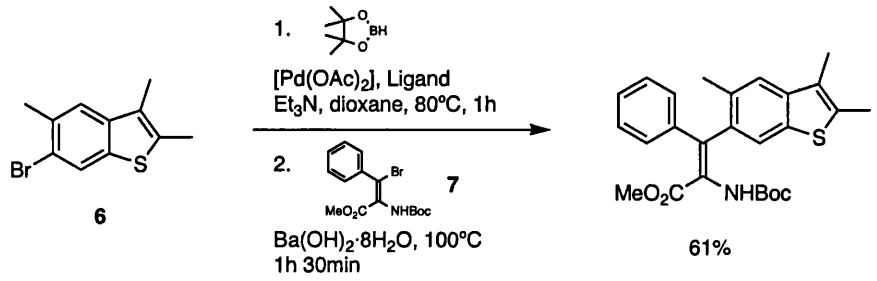
A major interest of organic chemistry research is the synthesis of novel amino acids. With a number of unnatural α-amino acids displaying important biological functionalities,[11,12] the demand for peptide based drugs is set to continue increasing in the coming years. The search for new methodologies is a hot area of research, and the application of the Suzuki-Miyaura cross-coupling to form novel amino acids has not been overlooked, in the search for milder routes compatible with a range of functional groups and suited to the demands of library synthesis.

Queiroz and co-workers have prepared a range of novel amino acids and dehydroamino acids containing the benzo[*b*]thiophene moiety, through the Suzuki coupling of *S*-arylcysteine derivatives with benzo[*b*]thiophene boronic acids, in moderate to high yields.[13] Efficient coupling of the boronic acids and halides was achieved in a DME-water solution at 90°C using 10 mol% of $[Pd(PPh_3)_4]$ and Na_2CO_3 as base (Scheme 7).



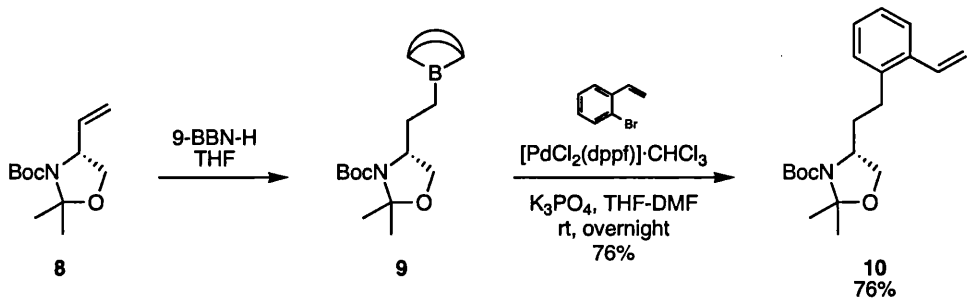
Scheme 7

Benzo[*b*]thienyldehydroamino acids can be prepared by the one-pot borylation and subsequent Suzuki coupling of bromobenzo[*b*]thiophenes **6** with analogues of **7**. Queiroz *et al.* have shown that the borylation of bromobenzo[*b*]thiophenes containing electron donating groups with pinacolborane, followed by the coupling with β-bromodehydroamino acid derivatives is an efficient method in the production in novel dehydroamino acids (Scheme 8).[14]



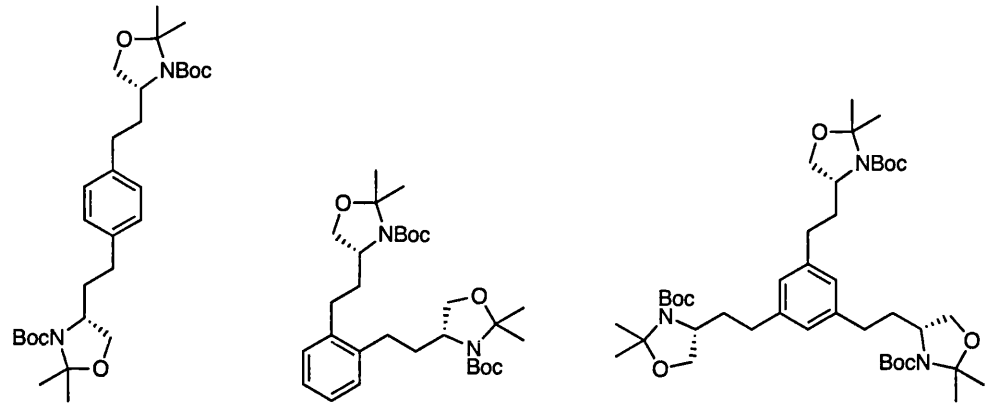
Scheme 8

Taylor *et al.* have investigated the preparation of homophenylalanine derivatives through a hydroboration-Suzuki cross coupling methodology.[12,15] Hydroboration of alkene **8** with 9-borabicyclo[3.3.1]nonane (9-BBN-H) afforded the organoborane **9**, confirmed by an oxidative workup (with H_2O_2/NaOH) which gave the corresponding alcohol. A variety of aryl and vinylhalides were efficiently coupled to organoborane **9** under mild conditions in moderate to high yields (Scheme 9).

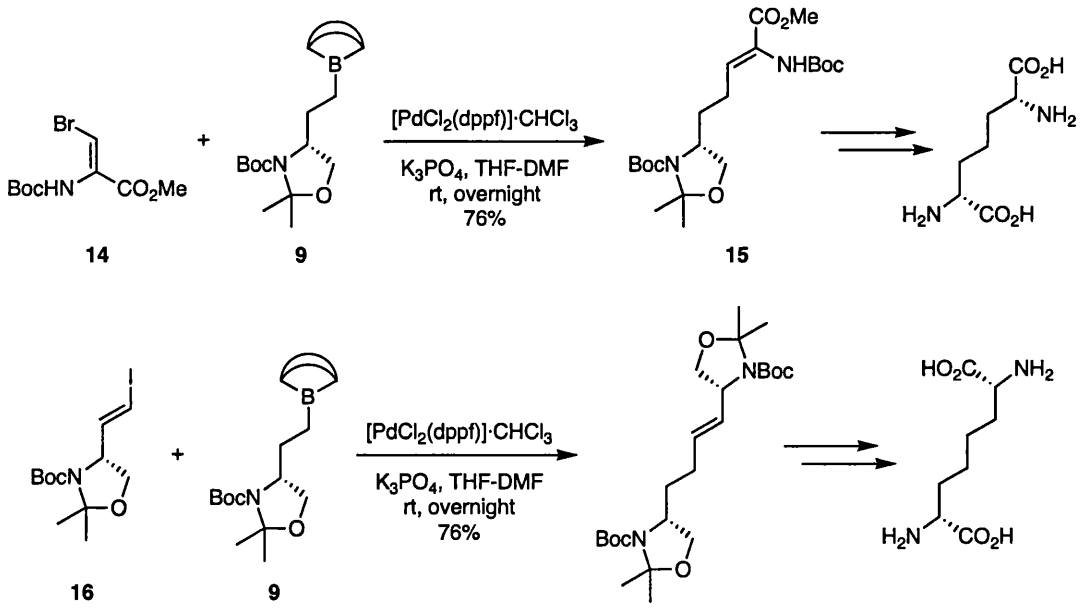


Scheme 9

The use of di- and tri-iodoarenes leads to double and triple coupling processes generating the potentially useful aryl scaffolds **11-13**. Cleavage and oxidation of the oxazolidinone, to afford the N-protected amino acids, can be achieved in a one-pot procedure using Jones' reagent.



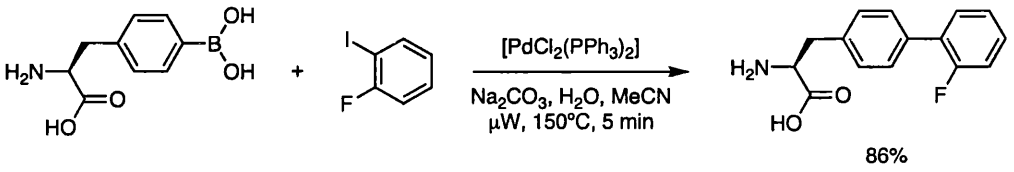
α,α'-Diamino diacids were also prepared using similar techniques. Coupling of the vinylhalides **14** and **16** to **9** gave the corresponding alkenes, which in the case of **15** can be asymmetrically hydrogenated and deprotected to yield the diamino diacids (Scheme 10).



Scheme 10

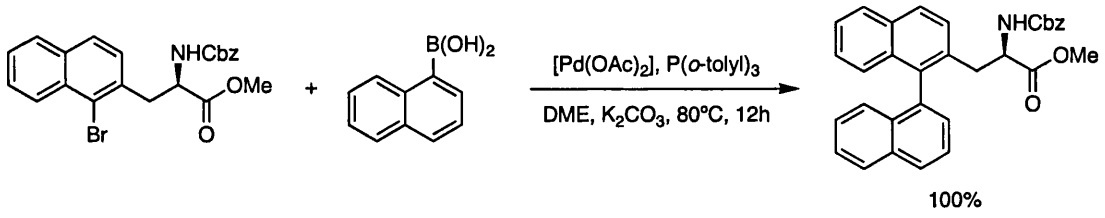
The synthesis of unprotected 4-aryl-phenylalanines, *via* a Suzuki coupling, has been presented by Gong and He.[16] Coupling of unprotected 4-boronophenylalanine with aryl halides was achieved in high yields in less than 10 minutes using microwave irradiation (Scheme 11). The direct coupling of the free amino acid under basic conditions appeared to safeguard the chiral centre from racemisation, often a concern when protected amino acids are involved in reactions at elevated temperatures. Indeed the

authors observed no significant scrambling of the sterogenic centre under the reaction conditions. A comparison reaction performed with traditional thermal methods yielded the product in a lower conversion (56%), compared to the microwave heated reaction (96%). Furthermore, the effect of switching positions of the boronic acid and halide in the coupling partners, gave a slightly reduced yield (75%), indicating this methodology can serve to compliment the original coupling.



Scheme 11

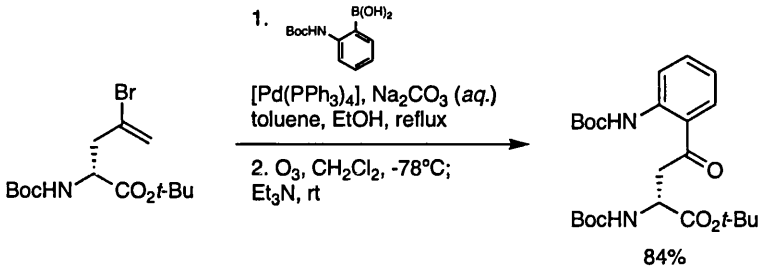
Hruby's group have studied the synthesis of phenylalanine, naphthylalanine and tryptophan analogues through application of the Suzuki cross coupling (Scheme 12).[17] The resultant amino acids, when incorporated into a peptide mimics, show increased selectivity for hMCR3 (human melanocortin receptors) over those peptides containing the simple amino acids. Although the authors note the production of atropisomers, no attempt was made to selectively form one or other by way of chiral ligands. The authors did however note that separation of the diastereomeric products was not possible by silica gel chromatography.



Scheme 12

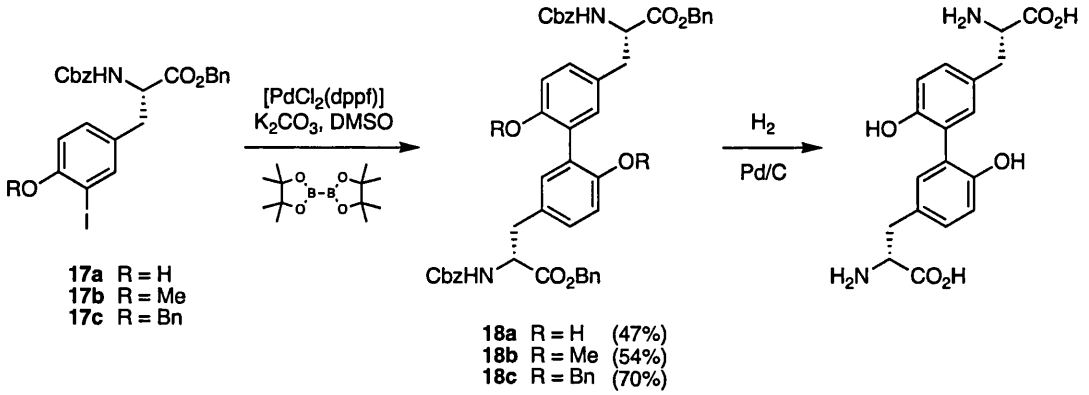
Aroylalanines have been associated with the kynurenine pathway, which is believed to play an important role in a variety of fundamental biological processes including: neuronal excitability, antioxidant status and cell growth/cell division. A number of aroylalanines derivatives have been shown to possess inhibitory properties for enzymes involved in this pathway. Lygo and Andrews have developed an efficient synthesis of these compounds,[18] through the Suzuki cross-coupling of the protected 2-amino-4-

bromopenten-4-enoic acid with a selection of arylboronic acids, subsequent oxidative cleavage, furnishes the desired aroylalanines in high yields (Scheme 13).



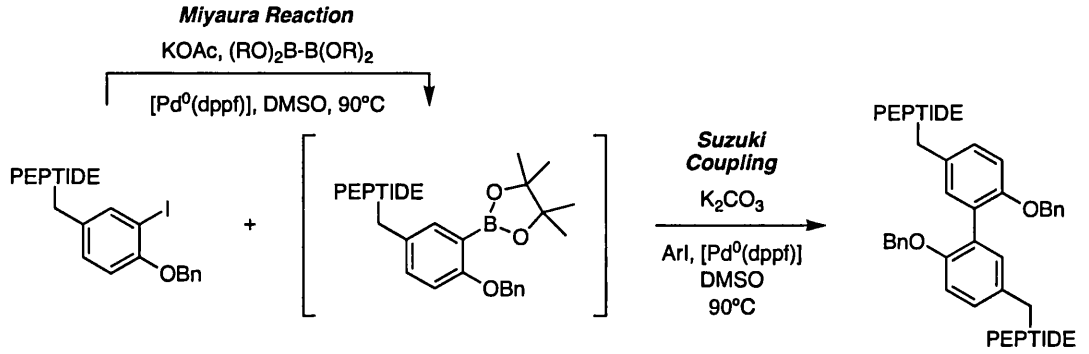
Scheme 13

Tyrosine-tyrosine cross-links in peptides have been identified as key chemical moieties in biochemistry. Tyrosine dimers formed by 3,3'-biaryl bond formation occur naturally in a plethora of living organisms,[19] including vertebrate proteins such as elastin and collagen,[19] fungal cell wall proteins,[20] insect egg[21] and sea-urchin envelopes.[22] It is thought that the tyrosine cross-linkage occurs as a defensive and/or strengthening role to the proteins.[23] The dimerisation of proteins through tyrosine is also believed to be necessary for proteins such as thyroglobulin, the precursor for the thyroid hormone thyroxine, to function properly.[24] Links have also been made between the formation of tyrosine cross links and clinical disorders such as Alzheimer's, Parkinson's, cystic fibrosis, atherosclerosis and cataract formation. Consequently interest in the formation of dityrosine both alone and within peptides is high. Building on the results by Zhu[25] and others Hutton and Skaff applied the Miyaura borylation-Suzuki coupling to the formation of dityrosine from iodotyrosine derivatives.[26] Primary studies investigated the individual Miyaura borylation and Suzuki reactions, with high yields when the phenolic alcohol was protected and low yields when present as the free alcohol. Since the dityrosine products formed are symmetrical the one-pot domino borylation-coupling was investigated (Scheme 14). Although in theory the addition of 0.5 equivalents of bis(pinacolato)diboron, should result in 50% of the idodide being converted to the boronate (which subsequently couples with the remaining iodide), in practice, the quantities required for conversion varied according to the differing rates of: conversion of the iodides to the boronate, protodeborylation and the Suzuki coupling, with values varying from 0.5 to 0.95 equivalents.



Scheme 14

Extension of this work to the synthesis of peptide dimers has been performed by Yoburn and Vranken.[27] Although the one pot Miyaura-Suzuki coupling was effective for cross linking short peptides (3 amino acids), longer chains required a stepwise process. Furthermore, it was found that two different bases were required for the individual steps; potassium acetate for the Miyaura reaction and potassium carbonate for the Suzuki coupling (Scheme 15).



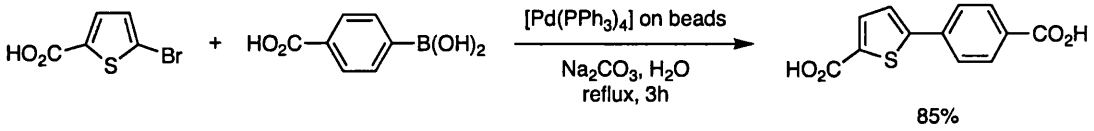
Scheme 15

Recent Advances: Heterogeneous Catalysts in Aqueous Medium

The ability to perform organic reactions in water is currently the subject of a vast amount of research, with the chemistry touted as "Green Chemistry" because of the reduction in the quantity of harmful organic solvents used for each reaction. To this end research concerned with the Suzuki-Miyaura reaction has been extended to study the use of solid supported sources of palladium in aqueous conditions. With the ability to

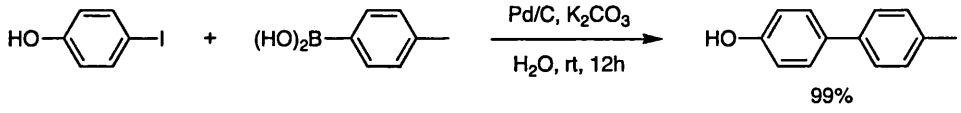
recycle the precious metal catalyst, this methodology is of great interest to industry where large quantities of both solvents and catalysts are currently required.

Recently Williams *et al.* have developed palladium on glass bead technology,[28] which displays high activity in the Suzuki cross coupling with minimal palladium leaching. Catalytically active glass beads were prepared by supporting triphenylphosphine onto derivatised glass beads *via* the treatment of beads with octyl trimethoxysilane in cyclohexane with heating. It is postulated that the catalyst is mobile within a thin film of cyclohexane around the bead, with the reaction occurring at the solvent interface. Successful Suzuki couplings were performed with a variety of aryl halides and boronic acids, by refluxing in a basic aqueous solution reaction times as short as 5 minutes were sufficient (Scheme 16).



Scheme 16

Work published by Sakurai *et al.* presents the common heterogeneous palladium catalyst, Pd/C, as a viable catalyst for the Suzuki-Miyaura reaction.[29] 4-Iodophenol can be efficiently coupled with a variety of aryl boronic acids in aqueous base at room temperature. Recovery of the catalyst is possible through filtration, with recovered Pd/C catalytically active after five cycles (89% yield), although the activity of the catalyst is depreciated slightly (Scheme 17).

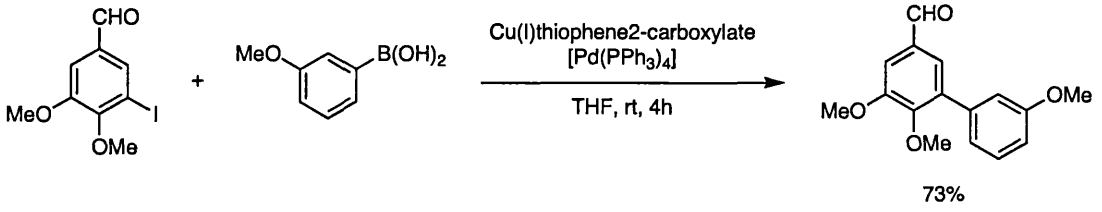


Scheme 17

Recent Advances: Neutral Conditions

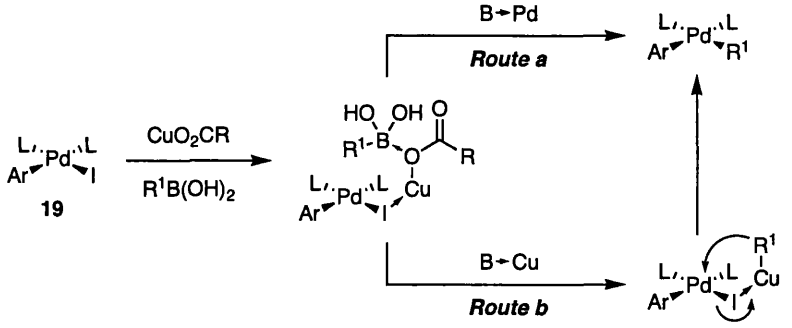
Although traditionally the Suzuki reaction must be performed in the presence of a base, Savarin and Liebeskind have published work to the contrary.[30] The addition of stoichiometric quantities of copper(I)thiophene-2-carboxylate (CuTC) to the reaction solution enables the coupling of aryl- and alkenyliodides with boronic acids at room

temperature under neutral conditions (Scheme 18). However, the cross-coupling was highly specific with no reaction observed with arylbromides, -chlorides and-triflates.



Scheme 18

The first step in the reaction is presumed to be the oxidative addition of the carbon-iodine bond to palladium providing the intermediate $ArPdL_2I$ **19**. CuTC mediated transmetallation with $R^1B(OH)_2$ must then occur. This transmetallation from boron to palladium can proceed either directly with the arylpalladium iodide-CuTC complex **route a**, or by prior boron to copper transmetallation **route b** (Scheme 19). The authors favour the former, direct transmetallation from boron to palladium, with CuI precipitating from the solution.

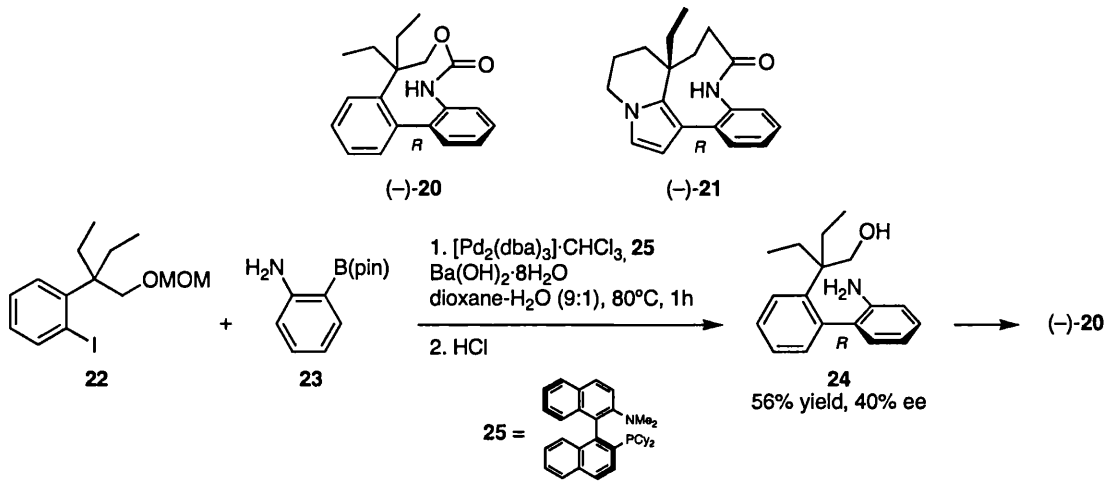


Scheme 19

Recent Advances: Chiral Suzuki-Miyaura Reactions

Although chiral Suzuki reactions are possible, examples are comparatively rare with their main application in the formation of atropisomers. The first application of the atropo-enantioselective Suzuki reaction to the synthesis of a biologically active axially-chiral biphenyl compounds was published by Baudoin's group earlier this year.[31] The synthesis of axially chiral bridged biaryl (–)-**20**, a structural analogue of the antimitotic (–)-Rhazinilam **21**, was achieved by the coupling of pinacolboronate **23** with aryl iodide **22** (Scheme 20). Although an array of conditions were evaluated, the use of $[Pd_2(dba)_3]$

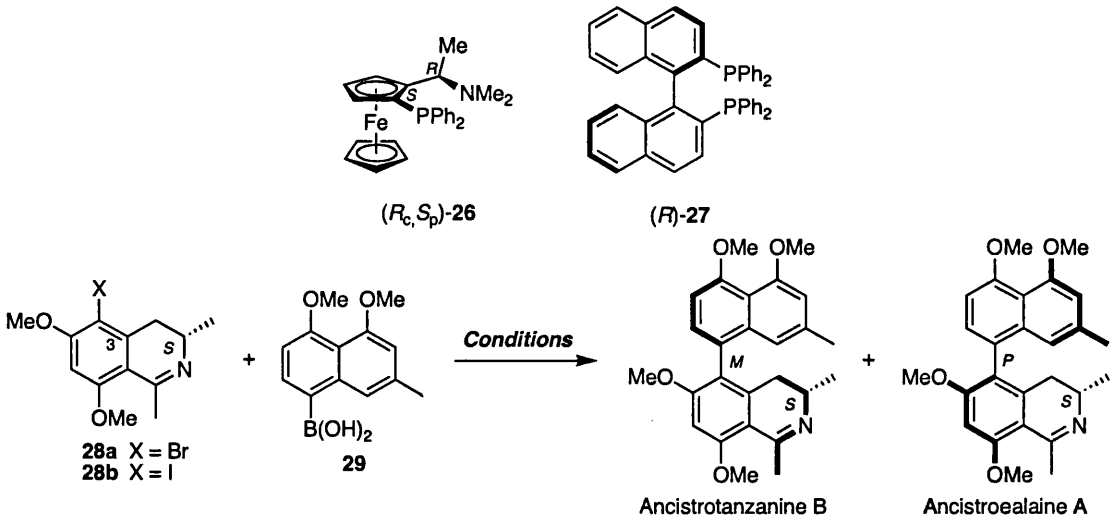
with $Ba(OH)_2$ as base in an aqueous dioxane mixture gave the best results. The reaction was performed at 80°C for 1 hour so as to prevent racemisation of the product. Ligand **25** (reported by Buchwald[32]) gave **24** in highest enantioselectivity (40% ee) with a yield of 56%. After conversion to carbamate (–)-**20**, by reaction with trisphosgene, the *R*-enantiomer could be isolated by crystallisation in 92% ee and 35% yield.



Scheme 20

Bringmann *et al.* have investigated the synthesis of the diastereomers of Ancistroealaine A and Ancistrotanzanine B[33] (Scheme 21). Isolated from the central African Liana *Ancistrocladus ealaensis* these compounds display antimalarial activity of a high standard. The coupling of the 1-naphthaleneboronic acid **29** with dihydroisoquinolines **28a** and **28b** was achieved in moderate yield in a range of reaction conditions (Table 1). The occurrence of any reaction is surprising given the presence of the free imino group on **28a** and **28b**. Although the isolated yield when coupling the bromo dihydroisoquinoline was low, exchange of the bromine with iodine increases to the yield to a moderate 50% (Table 1, entry 2), with a surprisingly low natural diastereomeric ratio of 55:45 in favour of the *P*-atropisomer. Application of the chiral ferrocene based catalyst (R_c,S_p)-**26** with $[Pd_2(dba)_3]$ gave a diastereomeric ratio of 75:25 with a preference opposite to that with an achiral catalyst. Although the authors predicted this would be the "mismatched" case, and that use of (S_c,R_p)-**26** would give a better ratio, in favour of the *P*-atropisomer. This was not however the case with no preference for either of the diastereoisomers when ligand (S_c,R_p)-**26** was used (Table 1, entry 4). Use of the two enantiomers of BINAP **27** gave contrasting results. With (*R*)-**27**

affording the *M*-isomer in a dr of 61:39, and (*S*)-**27** unexpectedly affording the same selectivity in an even higher isomeric ratio of 75:25.

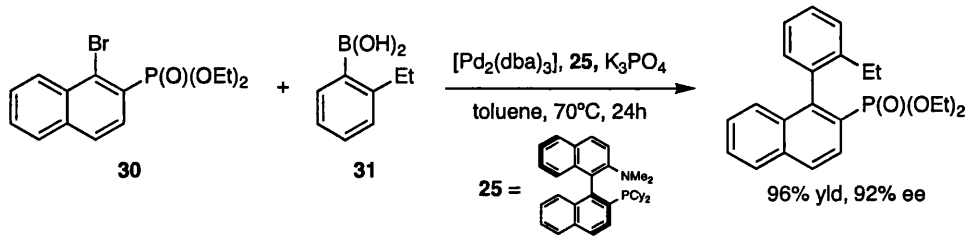


Scheme 21

Table 1 Coupling conditions, yields, and diastereomeric ratios for the synthesis of Ancistrotanzanine B and Ancistroealaine A *via* Suzuki couplings

Entry	Halide	Conditions	Yield (%)	*M(R):P(S)*
1	**28a**	toluene, K_3PO_4, $[Pd(PPh_3)_4]$	traces	n.d.
2	**28b**	toluene/H_2O, $NaHCO_3$, $[Pd(PPh_3)_4]$	50	45:55
3	**28b**	Toluene-H_2O, $NaHCO_3$, $[Pd_2(dba)_3]$, (***R*c,*S*p)-26**	38	75:25
4	**28b**	Toluene-H_2O, $NaHCO_3$, $[Pd_2(dba)_3]$, (***S*c,*R*p)-26**	34	51:49
5	**28b**	Toluene-H_2O, $NaHCO_3$, $[Pd_2(dba)_3]$, **(M(*R*))-27**	45	61:39
6	**28b**	Toluene-H_2O, $NaHCO_3$, $[Pd_2(dba)_3]$, **(P(*S*))-27**	50	75:25

Buchwald has synthesised chiral biaryl compounds, from the cross-coupling of bromonaphthalene **30** with phenylboronic acid **31**, in up to 92% ee *via* a catalytic Suzuki-Miyaura cross-coupling, using the binaphthyl-based electron-rich mono-phosphine ligand **25** (Scheme 22).[32]

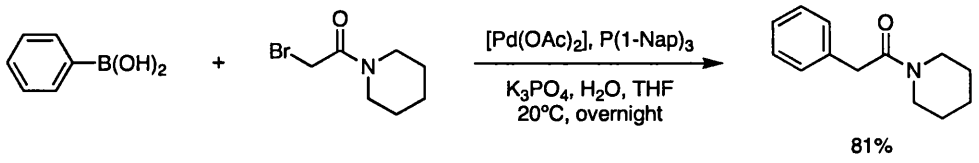


Scheme 22

Recent Advances: Miscellaneous

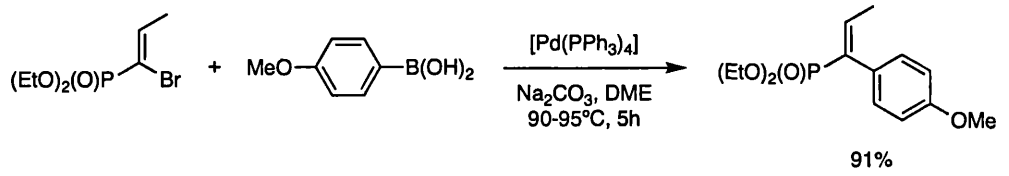
Recently there has been a great deal of interest in extending transition metal catalysed reactions to the coupling of highly functionalised compounds. Perhaps some of the most significant in terms of the Suzuki reaction are those published by Asensio, Gooßen and Kobayashi.

Gooßen's work dealt with the synthesis of aryl acetic acid derivatives from α-halocarbonyl derivatives and arylbornic acids.[34] α-Bromoacetic esters and α-bromoacetic amides were effectively coupled with arylboronic acids and esters in high yields (Scheme 23). Electron poor, bulky phosphine ligands were found to catalyse the reaction most efficiently, with K_3PO_4 as base. Luo and co-workers have since reported the coupling of aryldioxaborolanes with 2-bromo-*N*,*N*-dimethylacetamide using the basic phosphine ligand tricyclohexylphosphine, PCy_3.[35]



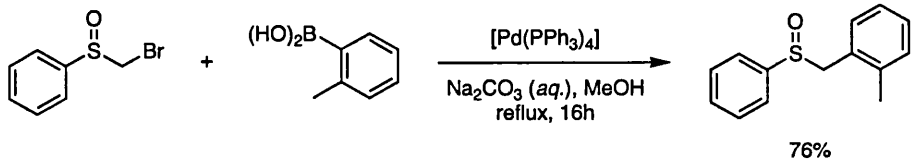
Scheme 23

The synthesis of α-arylalkenylphosponates was published by Kobayashi and William.[36] Both (*E*) and (*Z*)-isomers of α-bromoalkenyl phosphonates were coupled with arylboronic acids in high yields, with retention of stereochemistry throughout. The phenylations proceeded successfully with $[Pd(PPh_3)_4]$ and Na_2CO_3 when heated to 90-95°C for 5h in a DME solution (Scheme 24). Interestingly, attempts at the alkenylation with heptenylboronic acid failed under a variety of conditions.



Scheme 24

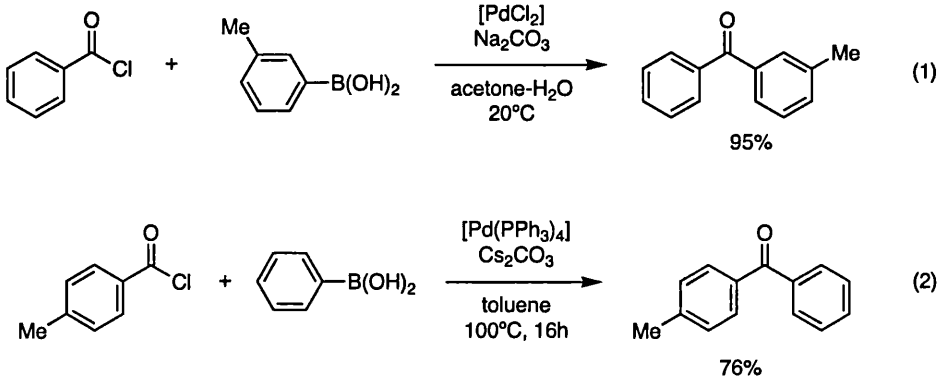
Arylation of α-bromo sulfoxides with boronic acids *via* palladium catalysis has recently been achieved by Asensio and co-workers,[37] in a system analogous to that of Gooßens for α-halo carbonyl derivatives. However, unlike the α-bromocarbonyl systems, where bulky phosphines are required, triphenylphosphine is an adequate ligand for sulfoxides (Scheme 25). α-Bromoethyl sulfoxide was also successfully coupled in moderate yields, although, the authors made no comments with regards to the enantioselectivity of the reaction.



Scheme 25

Recent Advances: Ketone Synthesis

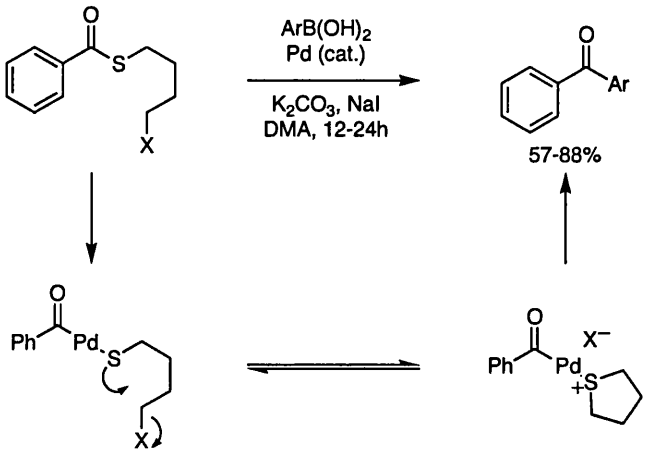
Modification of the Suzuki reaction to include the palladium catalysed coupling of acid chlorides with organoborates to provide the corresponding ketones, was first reported by Uemura and co-workers in 1993 through the reaction of sodium tetraphenylborate ($NaBPh_4$) with acid chlorides in THF at 25°C in the presence of $[Pd(PPh_3)_4]$.[38] Although with this early work just one of the four phenyl groups in the borate was available for transfer, Bumagin and Korolev later reported the successful transfer of all four aryl groups, with a phosphine-free $[Pd(OAc)_2]$ catalysed procedure in acetone.[39] Furthermore, boronic acids can be efficiently coupled with acylchlorides both in aqueous (Scheme 26 (eq.1)[39]) and anhydrous conditions (Scheme 26 (eq.2.)[40]).



Scheme 26

Whilst acid chlorides readily undergo oxidative addition to palladium they are too reactive to be broadly useful in sensitive, functionally rich systems. To date two methods have been developed to circumvent this problem, one by Liebeskind and the other by Gooßen.

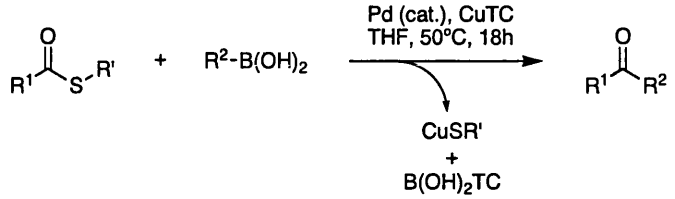
Liebeskind has reported the application of thiol ester-boronic acid cross coupling reactions. Although the carbon-sulphur oxidative addition to palladium is facile, the stable bond between the catalytically active palladium and the soft sulphur atom stops the reaction turning over. However, alkylative conversion of the palladium-thiolate bond to a labile palladium-thioether bond enables the catalytic cross-coupling to proceed.[41] Thus the reaction of 4-halo-*n*-butylthiol esters with arylboronc acids generated the associated cross-coupled products in high yields (Scheme 27).



Scheme 27

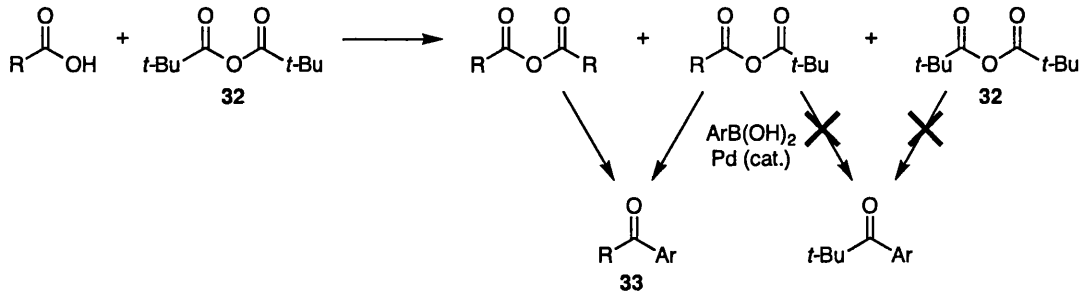
During, their studies Liebeskind and Srogl also established that simple thiol esters could be coupled under non-basic conditions by the addition of copper(I) thiophene-2-

carboxylate (CuTC).[42] In an analogous reaction to that described in Scheme 19 (on page 13) the copper facilitates the transmetallation from boron to palladium whilst at the same time removing the palladium bound thiolate by the generation of a copper-thiolate (Scheme 28).



Scheme 28

Gooßen and co-workers methodology focused on the coupling of boronic acids with carboxylic acids or anhydrides. Early work used the unreactive nature of the sterically demanding pivalic anhydride **32** to good effect.[43] By reacting carboxylic acids with pivalic anhydride a mixed anhydride was formed, activating the sterically less hindered carboxylic acid. Oxidative addition of the mixed anhydride to palladium followed by transmetallation of the aryl portion from the boronic acids sets up the reductive elimination of the corresponding ketone **33** (Scheme 29). Later work by Gooßen highlighted the use of dimethyl dicarbonate as a replacement for pivalic anhydride, due to the problems associated with the isolation of the product ketones from the by-products derived form the pivalic anhydride activating agent.[44]

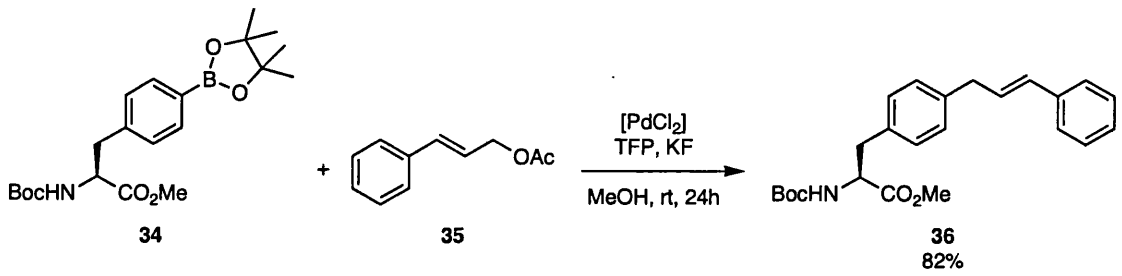


Scheme 29

1.2.2 Additional Palladium-Catalysed Cross-Coupling Reactions with Organoboranes

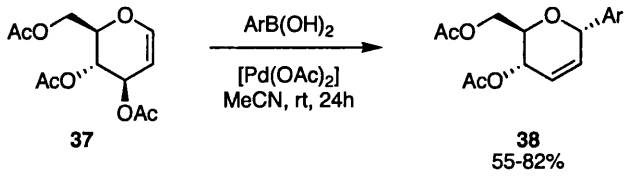
Allylic Substitution Reactions

Compared to the significant development of the Suzuki-Miyaura cross coupling, surprisingly only modest attention has been focused on the application of organoboron reagents in the palladium-catalysed allylic substitution reaction.[45] Recently the versatility of this reaction has been demonstrated by Ortar, who has reported the cross-coupling between a range of pinacol borates and allyl acetates.[46] For example the reaction of pinacol boronate **34**, with cinnamyl acetate **35** in the presence of palladium chloride, tri-2-furylphosphine (TFP) and potassium fluoride in a methanol solution afforded the desired phenyl alanine derivate **36** in 82% yield (Scheme 30).



Scheme 30

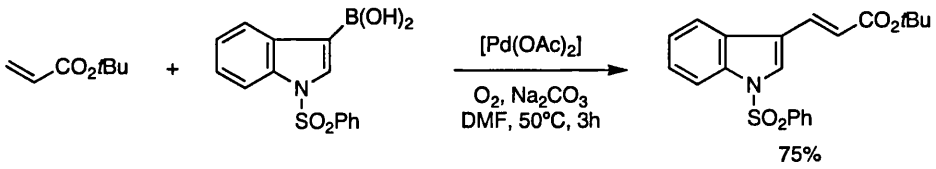
In a similar fashion *C*-glycosidation of peracetylated glycals can be performed by the palladium catalysed cross coupling of arylboronic acids with 3,4,6-tri-*O*-acetyl-D-glucal **37** (Scheme 31). However, rather than the oxidative addition of the C-O bond to the palladium prior to transmetallation with the arylboronic acid, the authors suggest that transmetallation occurs between the aryl boronic acid and the $[Pd(OAc)_2]$ forming the σ-aryl-Pd complex (Ar-Pd-OAc) occurs first. Subsequent *syn* addition to the α-face of the glycal double bond followed by *anti*-elimination of palladium(II) acetate to generate the carbon-Ferrier type product (*C*-arylglycopyranosides with an alkene in the 2,3-position) **38** in 55-82% yield.



Scheme 31

Heck-Type Reactions

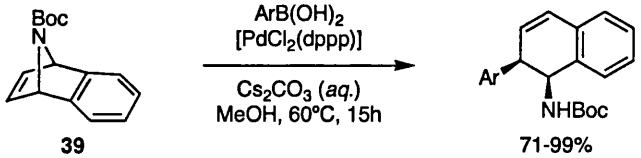
The Heck-type reaction of alkenes with organoboron reagents is also possible *via* palladium-catalysed mechanisms under oxidative conditions.[47] Jung and co-workers have recently published an efficient oxygen promoted Pd(II)-catalysed mechanism for the coupling of organoboron compounds with olefins (Scheme 32).[48] In general there was no significant effect on yields as a result of the nature of the group on the olefin. However, in the absence of oxygen, very low yields of the desired products were isolated.



Scheme 32

β-Heteroatom Elimination Reactions

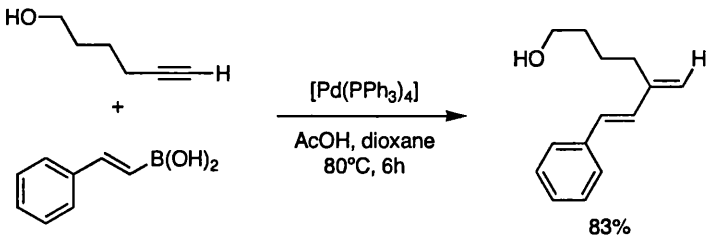
In the analogous reaction to that reported with rhodium[49] (Chapter 1.3.2), Lautens and Dockendorff have reported the palladium-catalysed ring-opening addition of arylboronic acids to heterobicyclic alkenes.[50] Whilst base was not required for the reaction to proceed, its presence did promote increased yields and reaction rates. The proposed mechanism occurs *via* a Heck-type addition to the alkene followed by β-heteroatom elimination leading to the ring-opened product, with palladium remaining in the +2 oxidation state throughout the catalytic cycle. Unlike the rhodium-catalysed reaction however, palladium effectively couples heteroarylboronic acids and azabenzonorbornadiene **39** (Scheme 33).



Scheme 33

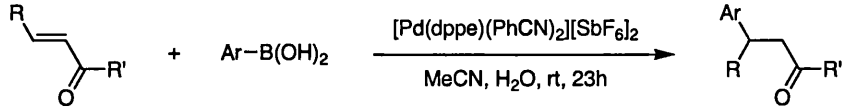
Hydroarylations

Similarly the hydroarylation reaction of alkynes with boronic acids, once restricted to rhodium catalysis, has been achieved using $[Pd(PPh_3)_4]$.[51] Oh *et al.* successfully coupled a range of mono- and disubstituted alkynes with aryl- and vinylboronic acids in high yield. Optimal conditions were found to be the heating of a 1,4-dioxane solution of alkyne with boronic acid in the presence of catalytic quantities of acetic acid and $[Pd(PPh_3)_4]$ at 80°C for 4-12h (Scheme 34). The acid additive was found to be necessary as its absence from the reaction led to a significant decrease in the reaction rate.



Scheme 34

The addition of boronic acids to enones, has been known to be catalysed by rhodium for a number of years *vide infra* (Chapter 1.3.1). Miyaura has recently reported the use of palladium to catalyse the same reaction. Hydroarylation products were generated upon reaction of arylboronic acids with enones, using $[Pd(dppe)(PhCN)_2][SbF_6]_2$ in an aqueous THF solution at room temperature for 23 hours (Scheme 35).[52] The authors note a marginal counterion effect with best results achieved with SbF_6.



Scheme 35

Like the analogous rhodium catalysed reaction the presence of water in the reaction media was found to be crucial, with a loss in reactivity in its absence. However, unlike the rhodium-catalysed reaction the addition to enals catalysed by palladium is selectively 1,4-addition with no 1,2-addition products observed. Although the palladium-catalysed reaction with α,β-unsaturated esters do occur they are typically slow in comparison to the rhodium-catalysed addition, with Heck-type products predominating.

1.3 RHODIUM-CATALYSED CROSS-COUPLING REACTIONS OF ORGANOBORON COMPOUNDS

1.3.1 1,4-Conjugate Addition of Organoboranes to Activated Alkenes

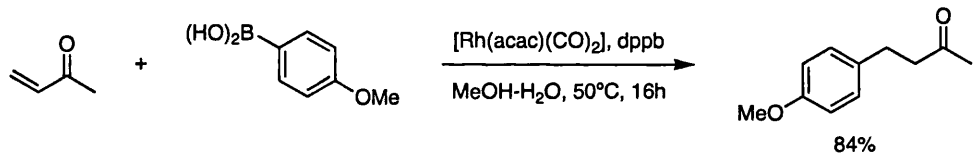
The 1,4-conjugate addition of organometallic compounds is a fundamental process in organic chemistry.[53] Involving the addition of nucleophiles to acceptor substituted double bonds and resulting in the formation of a new carbon-carbon bond, in principle a new stereogenic centre can be formed at both α and β carbons of the acceptor. The use of transition metal catalysts in combination with organometallic reagents has proved to be particularly effective for this important transformation. Traditionally, copper has found the broadest application, with various organocopper species widely used.[54] Frequently, Grignard reagents, organolithiums or diorganozincs are employed as the organometallic species, however, whilst they often provide high yields issues of chemoselectivity can limit their applicability. Of particular interest is the enantioselective 1,4-addition reaction where significant advances have been made; especially with copper catalysis of Grignard and diorganozinc reagents.[53-55] The rhodium-catalysed reactions of organoboron reagents presented in this section represent an attractive alternative to the copper-catalysed additions since they occur under mild conditions, are insensitive to water and can be performed with a wide range of substrates.

Additions to Enones

First reported in 1997 by Miyaura,[56] the rhodium catalysed 1,4-addition of aryl and alkenyl boronic acids to enones has received such a high level of interest there are almost no boundaries left in which to expand this methodology. A number of thorough reviews have been published on the rhodium-catalysed 1,4-addition reactions,[57,58] which comprehensively review a number of topics in more detail than shall be presented here. Indeed readers seeking an inclusive review on the mechanistic nature of the reaction are directed to Fagnou and Lautens review of 2003, and the references therein.[58]

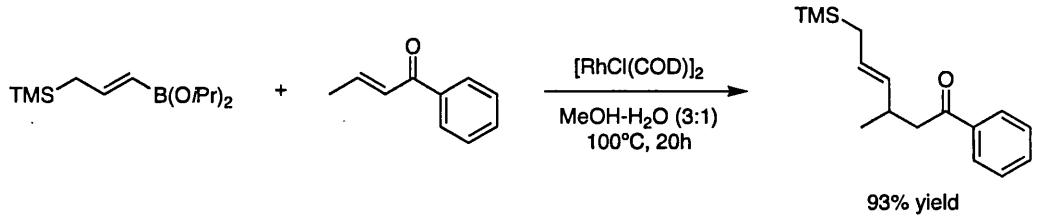
Miyaura and co-workers primary studies investigated the effect of phosphine ligands on the catalytic activity of $[Rh(acac)(CO)_2]$ in the 1,4-addition of aryl and alkenyl boronic acids to enones (Scheme 36). Whilst additions to methyl vinyl ketone (MVK) gave high

conversions (70-99%) for all ligands, the less reactive 2-octene-4-one revealed the order of dppb > dppp > trifurylphosphine(TFP) > dppe, PPh_3 and $AsPh_3$. This is indicative that the reaction is activated by an increase in the P-Rh-P angle. The reaction was not affected by the rhodium source with a range of rhodium complexes effectively catalysing the addition to MVK. The presence of water in the reaction was found to be essential for reactivity with a mixture of methanol and water being the most efficient medium for a range of boronic acids and enones. Little variation was observed in the coupled yields between boronic acids containing electron donating or withdrawing groups, however *ortho*-substituents were noted to hinder the reaction. Conjugate 1,4-additions to enals were also performed although the yields were lower (59% conversion) with the authors noting a decrease in reactions rates between these and the enones tested. Surprisingly the addition to cyclohexenone, an enone often used for asymmetric 1,4-additions, was low yielding, however no explanation was offered for this lack of activity. Interestingly, the addition of base hinders the reaction, the converse to that observed with the Suzuki reaction.



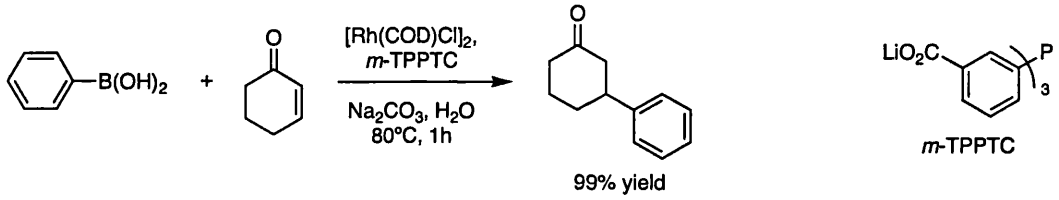
Scheme 36

A selection of functionalised boronates can be efficiently coupled *via* the rhodium-catalysed 1,4-addition. Miyaura has reported the successful addition of TMS functionalised boronates, as a viable route to the generation of functionalised allylsilanes containing a carbonyl group within the same molecule, which are intermediates for intramolecular allylsilylations.[59] The addition of (3-trimethylsilyl-1-propenyl)boronates to enones was achieved using $[RhCl(COD)]_2$ in an aqueous methanol solution in high yields (Scheme 37).



Scheme 37

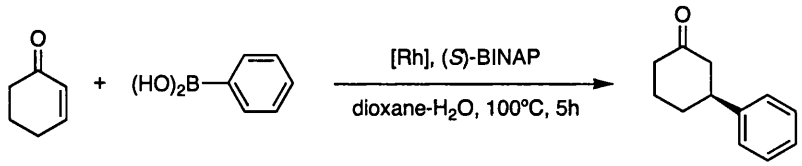
The conjugate addition reactions can be performed using solely water as a solvent as demonstrated by Genet's group.[60] Interestingly the addition occurs faster in the absence of a phosphine ligand and with added base, however, use of water-soluble ligands such as *m*-TPPTC does allow the rhodium catalyst to be recycled with no apparent loss in activity (Scheme 38).



Scheme 38

Additions to Enones: Enantioselective

In 1998 Hayashi and Miyaura jointly published the first asymmetric variant of this reaction.[61] Studying the addition to cyclohexenone, using the original conditions published by Miyaura it was observed that the use of chiral ligands resulted in a substantial loss of reactivity. However, application of $[Rh(acac)(C_2H_4)_2]$ with (*S*)-BINAP afforded the coupled product in 64% yield and 97% enantioselectivity when performed in aqueous dioxane at 100°C (Scheme 39). The reduction in the isolated yield of these reactions was attributed to the hydrolysis of phenylboronic acid to give benzene and boric acid in a competing reaction. This protodeborylation side reaction was especially pronounced for 4-methoxyphenylboronic acid. Higher yields of the addition products could be achieved by the use of a large excess of boronic acid. Both cyclic and acyclic *E*-enones can be efficiently coupled with aryl and alkenyl boronic acids. It is worth noting that the enantioselectivity was unaffected by the temperature of the reaction with the same selectivity obtained for a range of temperature between 40 and 120°C.

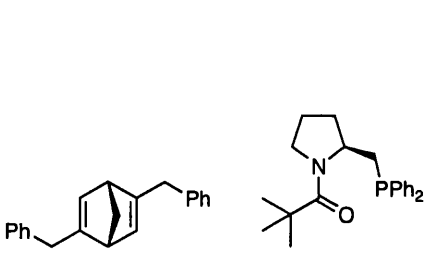


Rhodium Complex	$PhB(OH)_2$ (Equiv.)	Yield (%)	ee (%)
$[Rh(acac)(CO)_2]$	1.4	15	43
$[Rh(acac)(C_2H_4)_2]$	1.4	64	97
[Rh(acac)(*S*)-BINAP]*	1.4	62	97
$[Rh(acac)(C_2H_4)_2]$	2.5	93	97

* Isolated [Rh(acac)(*S*)-BINAP] was used as a catalyst

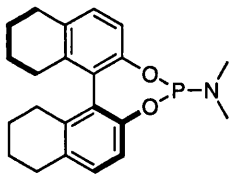
Scheme 39

Although BINAP was the first chiral ligand to be applied to the reaction a vast range of ligands have since been applied with varying efficiency, typically superior enantioselectivities are achieved with bidentate phosphines.[62] Ligands generating high enantioselectivities include: chelating dienes **40**,[63] amidomonophosphines **41**,[64] monodentate phosphoramidites **42**,[65-67] atroisomeric phosphines **(*S*)-P-Phos**[68] and **(*R*)-Digm-BINAP**[69] and diphosphites such as **43**[70].

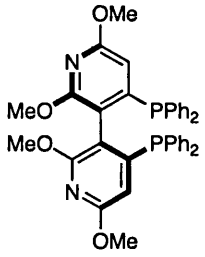


(*R,R*)-40
94% yield
96% ee

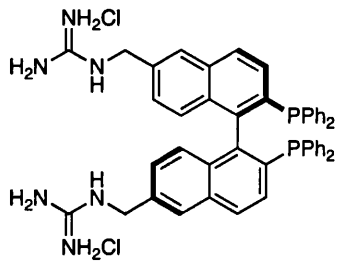
41
99% yield
96% ee



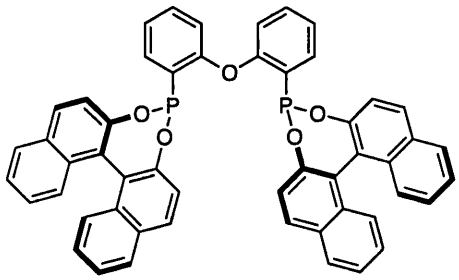
42
100% conversion
89% ee



(*S*)-P-Phos
99% yield
99% ee



(*R*)-Digm-BINAP
100% Yield
98% ee

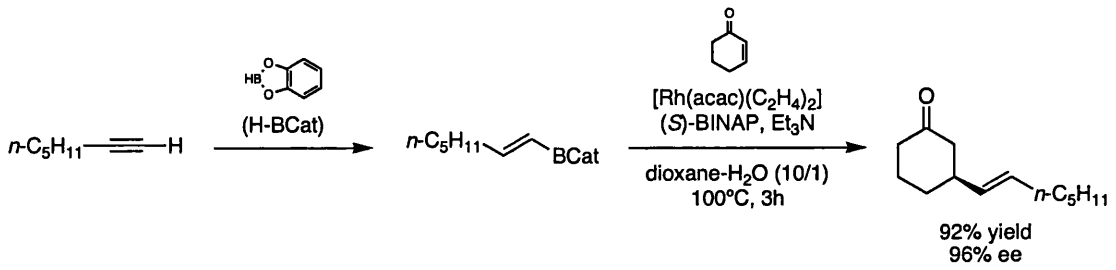


43
100% conversion
97% ee

Additions to Enones: Organoborane Sources

In addition to boronic acids other organoboranes have been efficiently utilised in the rhodium-catalysed 1,4-conjugate addition reaction including: boronic esters, lithium borates and potassium trifluoroborate salts.

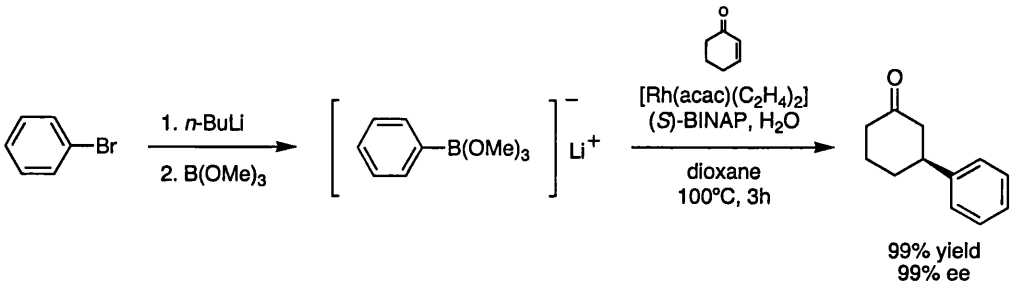
Hayashi and co-workers have reported the efficient addition of 2-alkenyl-1,3,2-benzodioxaboroles, prepared by the hydroboration of alkynes with catecholborane, to α,β-unsaturated ketones.[71] Application of the previously presented conditions for aryl and alkenyl boronic acids [Rh(acac)$(C_2H_4)_2$] with (*S*)-BINAP in a dioxane/water mix at 100°C) to the addition of (*E*)-1-heptenylborane, prepared by the hydroboration of 1-heptyne, to 2-cyclohexenone afforded only 29% of the 1,4-addition product, however a high enantioselectivity was achieved (94%). The low yield was attributed to the more acidic nature of the reaction medium caused by hydrolysis of the alkenyl catecholboranes, forming the alkenylboronic acid and catechol. Thus addition of base to the reaction mixture was postulated to improve the isolated yield. The addition of triethylamine significantly improved the chemical yield (92%) with no loss in enantioselectivity. Interestingly the addition of other bases did not produce matching characteristics, with chemical yields remaining low at 26-30%. The reaction proceeded most efficiently with 5 equivalents of borane to the alkene and 2 equivalents of triethylamine to the borane (Scheme 40). High yields and enantioslectivities were achieved for a variety of alkynes and enones using these conditions.



Scheme 40

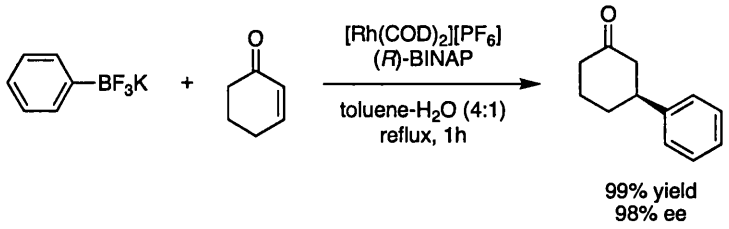
Addition reactions of lithium trimethyl arylborates, readily prepared from aryl bromides by lithiation followed by treatment with trimethoxyborane, to enones are also viable (Scheme 41).[72] The reaction can be performed in 'one pot synthesis' avoiding the need for the isolation of the boronic acids, with superior yields obtained when compared to those with the corresponding boronic acids. It should be noted that the reaction requires

just one equivalent of water to the boronate. Due to the lack of the competing protodeborylation reaction 4-methoxyphenyl can be efficiently coupled under these conditions. It is assumed that the active species is one of $Li[PhB(OMe)_2(OH)]$ or $PhB(OMe)(OLi)$ together with methanol, since the reaction does not proceed with $PhB(OMe)_2$, until 1 equivalent of lithium hydroxide was added.



Scheme 41

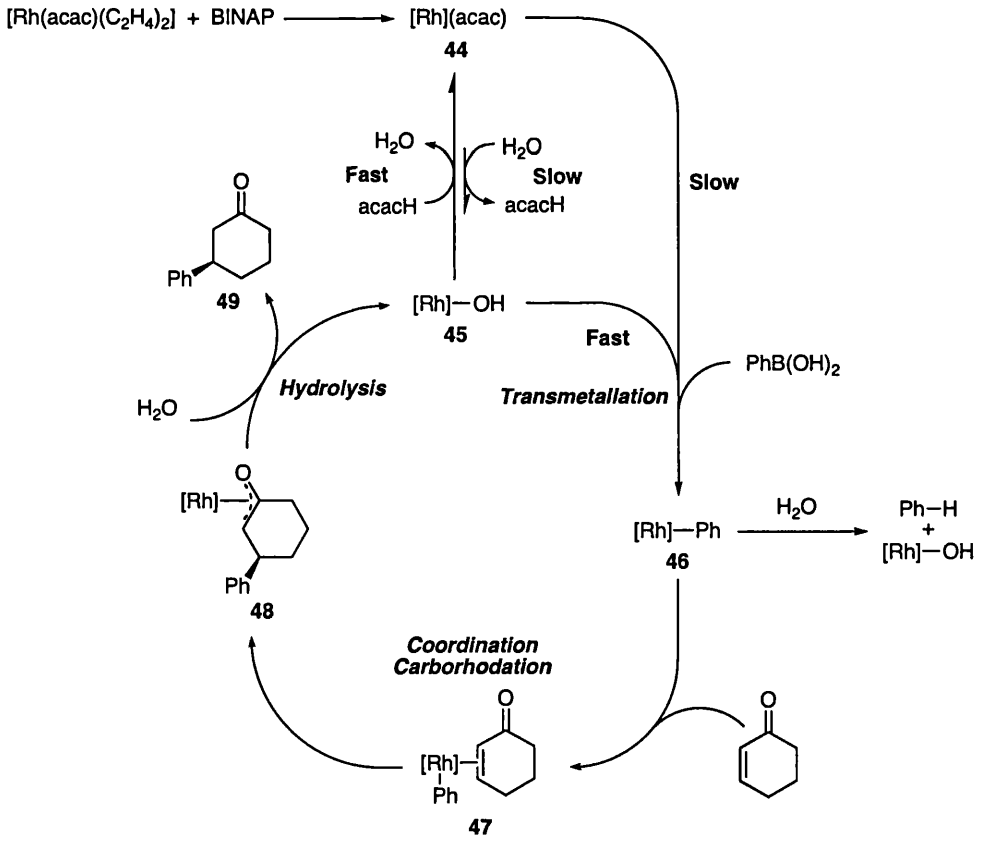
Primary studies by Batey *et al.* with potassium trifluoroborate salts, indicated that Miyaura's original conditions (those of $[Rh(acac)(CO)_2]$ with dppb in aqueous methanol as solvent at 50°C) were effective for the racemic reaction.[73] The enhanced stability of these reagents, added to the increased reactivity means a much broader range of aryl and alkenyl groups can be coupled under milder conditions. Genet has since extended the use of this boronate to the asymmetric 1,4-addition reaction.[74] In the presence of cationic rhodium complex prepared *in situ* from $[Rh(COD)_2][PF_6]$ and (*R*)-BINAP in a toluene-water mix at 110°C, the 1,4-addition of potassium phenyltrifluoroborate to 2-cyclohexene proceeded in 99% yield and 98% enantioselectivity (Scheme 42). The reaction of potassium trifluoroborate salts has some characteristic properties that differ greatly from the reaction with boronic acids; firstly, the reaction is best catalysed by complexes formed from cationic rhodium salts, such as $[Rh(COD)_2][OTf]$, $[Rh(COD)_2][BF_4]$, $[Rh(COD)_2][PF_6]$ and $[Rh(COD)_2][ClO_4]$, with complexes formed from neutral species such as $[Rh(acac)(C_2H_4)_2]$ failing to efficiently catalyse the reaction. Secondly, whilst the yield is generally unaffected by the solvent used the enantioselectivity is highly dependent on the solvent system, with aprotic and non-chelating solvents preferred with an excess of water. However the addition of too much water does slow the reaction rate, with no product formed in neat water. Genet and co-workers have successfully coupled a variety of borate salts with high enantioselectively, including 4-methoxyphenyl-, 3-thiophenyl- and alkenyl-borates.



Scheme 42

Mechanistic Studies

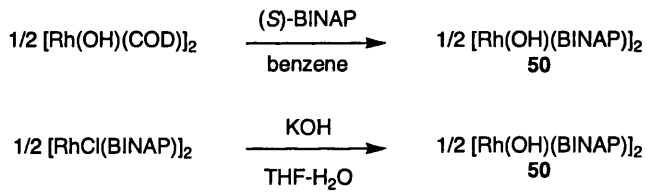
Although the mechanism was eluded to in the primary publication by Miyaura,[56] it wasn't until Hayashi isolated key intermediates in 2002 that the original postulation was confirmed.[75] A detailed review of the 1,4-addition mechanism and rhodium catalysed C-C bond forming reactions in general has recently been published by Fagnou and Lautens.[58]



Scheme 43

The catalytic cycle essentially consists of three main steps: 1) Transmetallation of the aryl/alkenyl species to the rhodium centre from the boronic acid to form the phenyl rhodium **46**; 2) Coordination/insertion of the enone to form the oxy-π-allyrhodium **48**; and 3) Hydrolysis of **48** to afford the desired 1,4-addition product **49** and regenerate the active hydroxorhodium catalyst **45** (Scheme 43). Hydrolysis of the oxa-π-allyl rhodium complex could occur by two possible routes: one through the oxidative addition of water to the rhodium generating a $Rh^{III}(H)(OH)R$ species followed by reductive elimination to give the formal protonolysis products R-H; or by direct hydrolysis of the rhodium oxa-π-allyl species followed by coordination of the hydroxide anion. As yet neither of these routes have been conclusively proven or disproven.

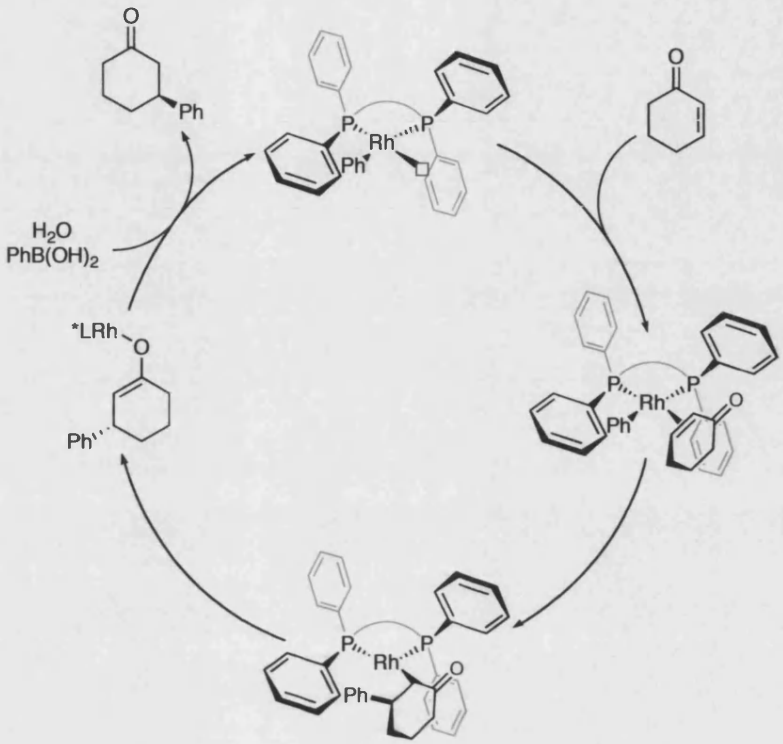
Whilst these three steps can be performed individually at 25°C, when the catalytic addition of phenyl boronic acid to 2-cyclohexenone (Scheme 39) is performed the reaction does not proceed below 80°C. It was later established that the transmetallation of the phenyl group from boronic acid is very slow for [Rh(acac)(BINAP)] **44**, whilst conversion of hydroxorhodium complex **45** to [Rh(acac)(BINAP)] **44** was observed to be instantaneous upon the addition of acetylacetonate. Later investigations by Hayashi[75] and others[66] showed the catalytic reaction could be performed at ambient temperatures by using the preformed rhodium hydroxide complex $[Rh(OH)(BINAP)]_2$ **50** prepared from either $[Rh(COD)(OH)]_2$ or $[RhCl(BINAP)]_2$ (Scheme 44).



Scheme 44

Scheme 45 presents the proposed stereochemical pathway for the reaction catalysed by rhodium complexed with (*S*)-BINAP. It is known that transition metals coordinated with BINAP posses a highly skewed structure,[76] and rhodium coordinated with (*S*)-BINAP should contain an open space in the lower right hand quadrant of the vacant coordination site, the upper being blocked by one of the phenyl rings of BINAP. The alkene double bond of 2-cyclohexenone coordinates to the rhodium *via* its 2 *si* face, with the ketone projecting into the vacant quadrant. This intermediate undergoes migratory insertion to form a stereogenic centre with absolute configuration (*S*). All 1,4-

addition products when using (*S*)-BINAP should therefore have the same absolute configuration resulting from the addition to the 2 *si* face of enones and other electron deficient alkenes.



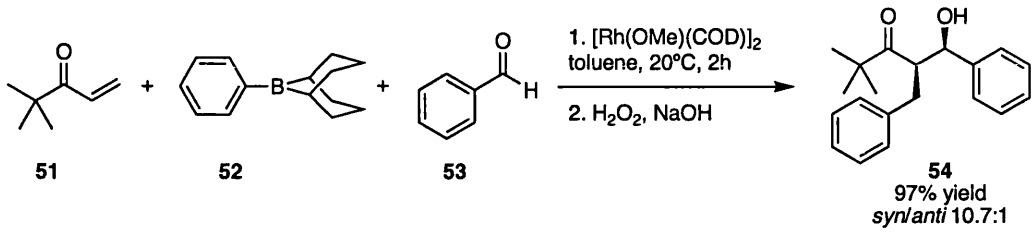
Scheme 45

Tandem 1,4-Addition-Aldol Reactions in Aprotic Solvents

Typically the presence of water, or other protic solvent, in the reaction medium is seen as an important addition for the catalytic cycle to proceed, as in the absence of water or other proton source the hydrolysis of the oxa-π-allyl rhodium species can not occur. Thus the catalytically active hydroxorhodium species and the hydrolysed 1,4-addition product would not be formed. However, although the addition of water is advantageous for the 1,4-addition reaction to proceed, it can also be a drawback giving solely the hydrolysed products.

Recently Hayashi has found that the use of 9-aryl-9-borabicyclo[3.3.1]nonanes (9-Ar-9-BBN), rather than boron reagents with the boron bonded to oxygen such as: boronic acids, *B*-arylcatchecolborane and *B*-arylpinacolborane, in anhydrous conditions enables further reactions to occur with the oxa-π-allylrhodium intermedite.[77,78] Thus the addition of benzaldehyde **53** to a mixture of 9-phenyl-9-BBN **52**, *tert*-butyl vinyl ketone **51** and

$[Rh(OMe)(COD)]_2$ in toluene, followed by an aqueous oxidative workup yields the tandem 1,4-addition-aldol product **54** in 97% yield with high *syn* selectivity (*syn*/*anti* 10.7:1) (Scheme 46). In the absence of benzaldehyde no reaction was observed, suggesting that the catalytic cycle did not turn over.

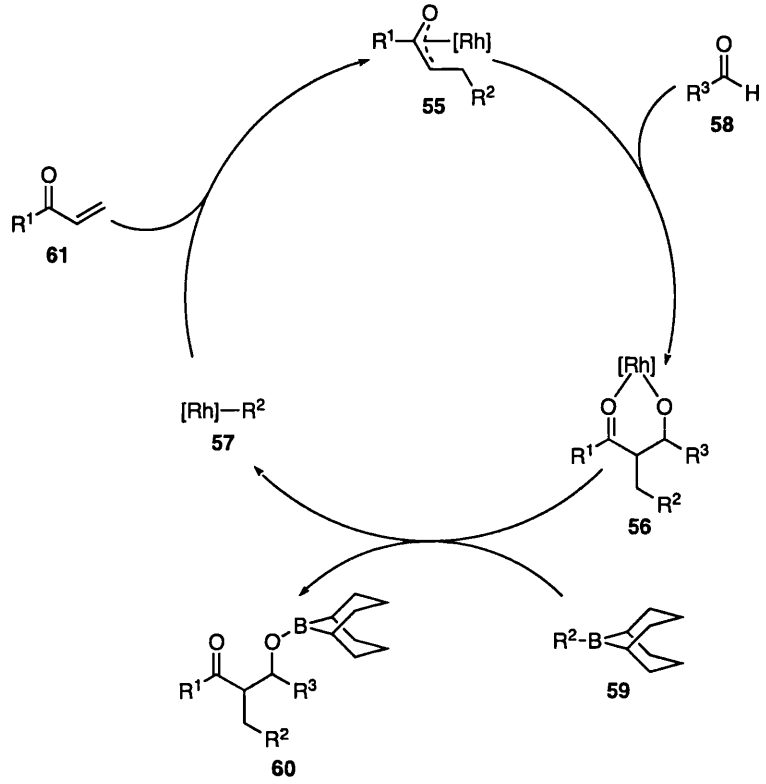


51 **52** **53** **54**
97% yield
syn/*anti* 10.7:1

Scheme 46

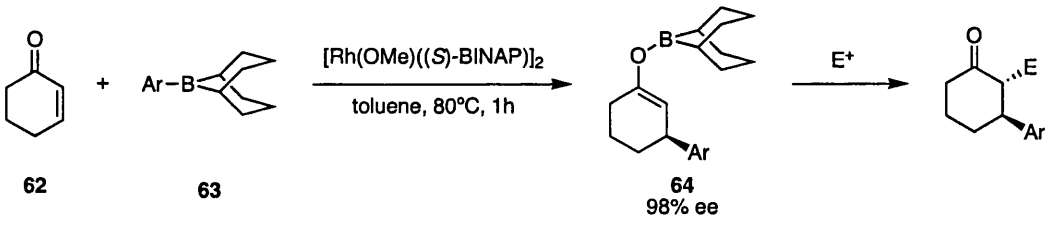
The mechanism for this tandem addition-aldol reaction is thought to proceed as displayed in Scheme 47. Addition of *B*-Aryl-9-BBN **59** to enones **61** proceeds in the same way as the standard 1,4-addition with the formation an intermediary oxa-π-allylrhodium species **55**. Due do the absence of a proton source **55** reacts in an aldol fashion with aldehyde **58** to form the rhodium aldolate **56**. Which undergoes direct transmetallation with the aryl or alkenyl group from 9-BBN **59** to give the boron aldolate **60** and regenerate the organorhodium intermediate **57**.

The asymmetric variant of this transformation was examined using [Rh(OH)((*S*)-BINAP)]$_2$. However, the hydroxy-rhodium-BINAP complex was not as active as $[Rh(OMe)(COD)]_2$ (44% and 72% yield respectively) for the reaction of **51**, with 9-(4-fluorophenyl)-9-BBN and propionaldehyde. The 1,4-addition-aldol product consisted of the *syn* isomer (41% ee (4*S*,5*R*)) and *anti* isomer (94% ee (4*R*,5*R*)) in a ratio of 0.8 to 1.



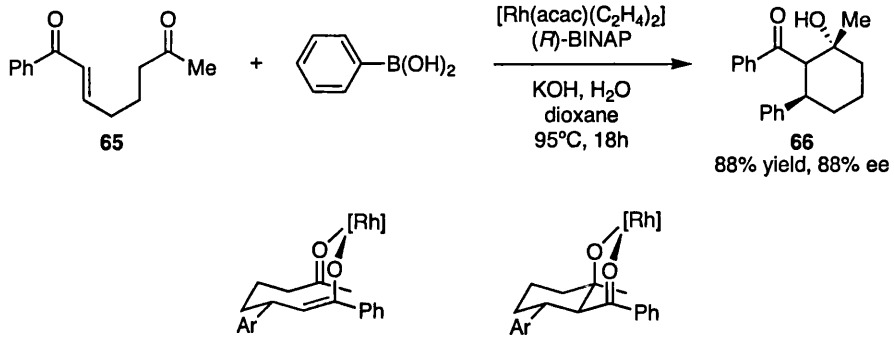
Scheme 47

Hayashi later published results showing that when 2-cyclohexenone **62** was reacted with 9-aryl-9-BBN **63** in the absence of aldehyde in toluene at 80°C with [Rh(OMe)((*S*)-BINAP)]$_2$, the chiral boron enolate **64** is generated.[77] Subsequent reaction of the boron enolates with a range of electrophiles gave near perfect *trans* selectivity (Scheme 48).



Scheme 48

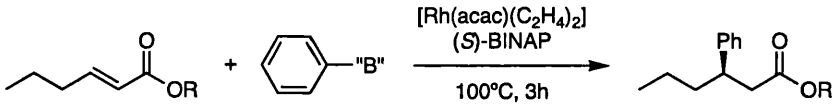
The intramolecular tandem 1,4-addition-aldol reaction of enone-ketone **65** with phenyl boronic acid was reported to proceed in the presence of excess water by Krische (Scheme 49).[79] Because the intramolecular reaction with the ketone is faster than protonolysis with water, the tandem 1,4-addition-aldol cyclisation product **66** is formed even in the presence of water. The stereochemistry observed can be accounted for by the Zimmerman-Traxler type transition state of the (*Z*)-enolate.



Scheme 49

Additions to Esters

Extension of the primary work with enones to the reaction of acrylates revealed a loss in reactivity when compared to the corresponding enones. Initial reports by Hayashi[80] and subsequently Miyaura[81] highlighted the successful formation of chiral β-arylesters from α,β-unsaturated esters. Interestingly, whilst the addition of boronic acids to linear esters proceeds without problems for the smaller methyl and ethyl esters, the chemical yield is found to be markedly reduced for the bulkier *iso*-propyl and *tert*-butyl esters. However, the use of lithium phenylborate gave high yields for the additions to all of the acrylates screened (Scheme 50). Cyclic esters, conversely, behave in the opposite fashion with higher yields afforded from the use of boronic acids (94%) than with lithium borates (38%); with both methods generating the products in high enantiopurity. It should be noted however, that the enantioselectivity observed is more a function of the bulk of the ester moiety than of the β-subsistent. Miyaura also observed the isolation of a small quantity of the Heck-type alkene product from the racemic reaction with $[Rh(COD)(MeCN)_2][BF_4]$. It is proposed that this alkene product is generated by β-hydride elimination from a species containing the rhodium bound to the α-position of the enolate.



Method A:
$PhB(OH)_2$ (5.0 equiv.)
in dioxane-H_2O (10:1)

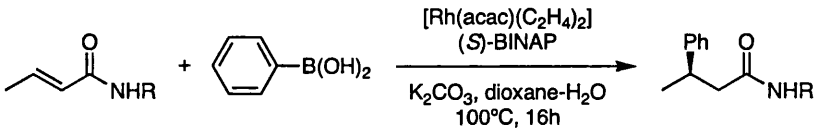
Method B:
$LiPhB(OMe)_3$-H_2O (1:1) (2.5 equiv.)
in dioxane

R = Me:	Method A	94% yield, 86% ee
	Method B	>99% yield, 89% ee
R = Et:	Method A	>99% yield, 90% ee
	Method B	>99% yield, 91% ee
R = *i*-Pr:	Method A	42% yield, 94% ee
	Method B	96% yield, 95% ee
R = *t*-Bu:	Method A	21% yield, 95% ee
	Method B	92% yield, 96% ee

Scheme 50

Additions to Amides

The 1,4-addition of boronic acids to α,β-unsaturated amides, suffers further loss of reactivity when compared to esters. Miyaura has reported the efficient use of the [Rh(acac)$(C_2H_4)_2$]/BINAP system for the 1,4-addition to α,β-unsaturated amides.[81,82] Although the reaction was found to suffer from incomplete conversion, the addition of a catalytic quantity of aqueous base improved yields considerably, often driving the reaction to completion. A variety of α,β-unsaturated amides can be coupled in this fashion (Scheme 51), however, no reaction was observed for *N*,*N*-dialkyl derivatives such as piperidine amide.



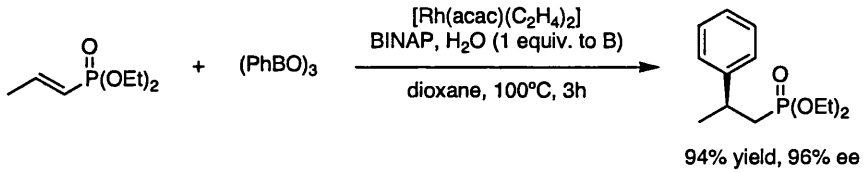
R =	H	62% yield, 89% ee
	Ph	88% yield, 90% ee
	Cy	80% yield, 93% ee
	CH_2Ph	85% yield, 93% ee

Scheme 51

Additions to Other Activated Alkenes.

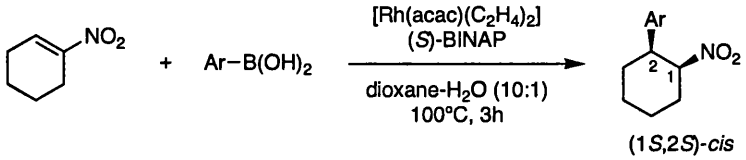
Hayashi has reported conjugate 1,4-addition of arylboronic acids to 1-alkenyl phosphonates, efficiently generating the corresponding β-aryl phosphonates in high yields and selectivity (Scheme 52).[83] Contrary to the previous rhodium-catalysed

additions with boronic acids the presence of water as a co-solvent was found to significantly reduce the catalyst activity. However, application of the cyclic anhydride of boronic acids (boroxine) with the addition of water (1 equivalent to boron) generated considerably improved activity with high isolated yields. The presence of a small quantity of water was essential for the catalyst to turn over, with just 5% yield recorded in the absence of water. The resultant alkylphosphonates containing the stereogenic carbon centre were effectively coupled *via* Horner-Emmons type reactions to afford optically active alkenes. It should be noted however, that the diethyl phosphonates required primary conversion to the diphenyl ester to enable the Horner-Emmons reaction to proceed efficiently. Remarkably, the use of either isomer of diethyl-1-propenylphosphonate (*Z*) or (*E*) both gave products where phenylation had occurred from the *si* face, indicating the dialkoxyphosphinyl moiety pays a key role in the enantiofacial selection.



Scheme 52

Electron deficient nitroalkenes also proved to be good substrates for the rhodium catalysed asymmetric conjugate 1,4-addition of arylboronic acids. Hayashi described the reaction of 1-nitrocyclohexene with phenylboronic acid in the presence of rhodium/(*S*)BINAP catalyst in aqueous dioxane at 100°C for 3 hours.[84] The desired 2-phenyl-1-nitrocyclohexane was generated in 89% yield with the main product being the thermodynamically less stable *cis* isomer (*cis*/*trans* = 87/13) in 99% ee (Scheme 53). Unfortunately the authors failed to examine the opposite enantiomer of ligand, (*R*)-BINAP, as this should have formed the more thermodynamically stable *trans* isomer. Should the *trans* isomer have been observed, the orientation of the proton source during the hydrolysis step would have been partially eluded to.

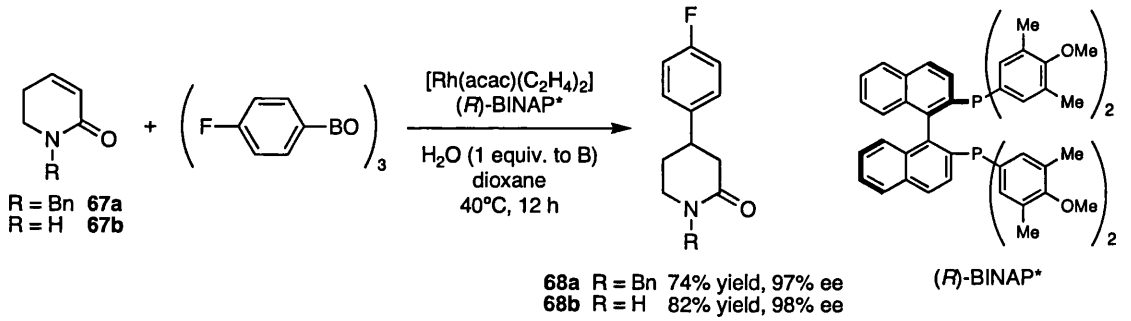


	yield %	*cis*/*trans*	% ee
Ar = Ph	89	87/13	98.5
4-MeC_6H_4	89	88/12	97.6
4-$CF_3C_6H_4$	88	85/15	99.0
3-ClC_6H_4	89	85/15	99.0
2-naphthyl	84	85/15	98.0
(*E*)-*n*-$C_5H_{11}CH$=CH	71	77/23	60.7

Scheme 53

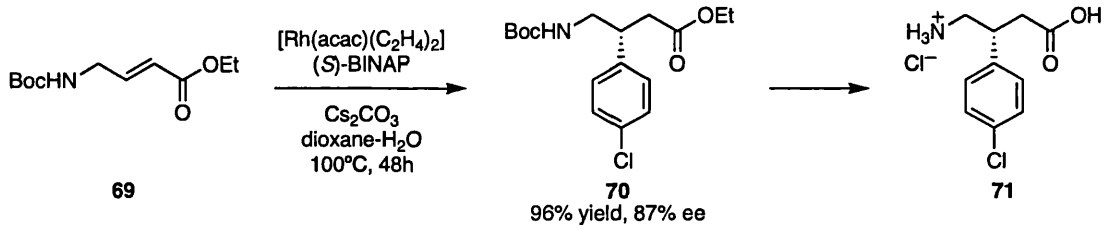
Applications in Organic Synthesis

Although this chemistry is still in it's infancy there have been some notable applications throughout organic synthesis. The first application of the rhodium-catalysed 1,4-addition of boronic acids to activated alkenes was that of the synthesis of 4-aryl-2-piperidinones, realised by the asymmetric addition of organoboron reagents to 5,6-dihydro-2(1*H*)-pyridinones.[85] The addition of a 4-fluorophenyl moiety produces compounds whose structures are key intermediates for the synthesis of biologically active compounds such as homologues of Baclofen, a selective agonist of the $GABA_B$ receptor. Interestingly the addition of 4-fluorophenylboronic acids to *N*-benzyl-5,6-dihydro-2(1-*H*)-pyridinone **67a** affords the desired product in significantly lower yield than when simple phenylboronic acid is applied (17 and 70% yields respectively) in aqueous dioxane at 100°C for 3 hours. This lower conversion was ascribed to the very rapid rate of hydrolysis of 4-fluorophenylboronic acid giving 4-fluorobenzene. Gratifyingly reduction in the quantity of water added to the reaction, the use of the cyclic anhydride (3-fluorophenylboroxine) and reduction in temperature to 40°C enabled the reaction to proceed in 63% yield, with high enantiomeric purity (97% ee). Modification of the BINAP ligand to (*R*)-BINAP* further increased the yield, to 74% (Scheme 54). The reaction of 5,6-dihydro-2(1*H*)-pyridinone **67b** was found to proceed more readily and with higher enantioselectivity than that of the *N*-benyl derivative **67a**, a finding which correlates with findings later published by Miyaura (*vide supra*, Scheme 51, on page 35).[82]



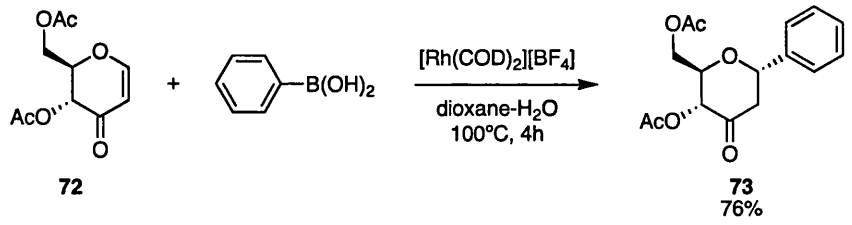
Scheme 54

Baclofen ((*R*)-4-amino-3-(4-chlorophenyl)-butyric acid) **71** has since been prepared using the rhodium catalysed conjugate 1,4-addition.[86] Treatment of the α,β-unsaturated-γ-aminbutyric acid ester **69** with 4-chlorophenylboronic acid in the presence of a rhodium complex formed from $[Rh(acac)(C_2H_4)_2]$ and (*S*)-BINAP with caesium carbonate as base in an aqueous dioxane solution gave the protected γ-aminbutyric acid **70**, in 96% yield and 87% ee (Scheme 55). A variety of boronic acids were added by this approach to form an array of analogous structures.



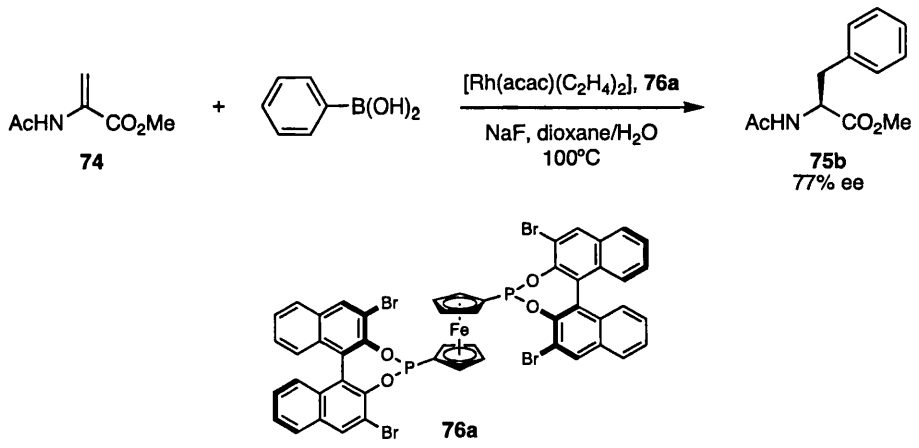
Scheme 55

The stereoselective formation of the α-anomer of *C*-glycosides by rhodium catalysed 1,4-addition of acetylated enones derived from glycals was reported by Maddaford in 2001.[87] Enigmatically the application of the neutral $[Rh(acac)(C_2H_4)_2]$ complex with various phosphine ligands did not generate the desired 1,4-addition product, neither did the use of other neutral Rh(I) catalysts. However, use of the cationic complex $[Rh(COD)_2][BF_4]$ does efficiently generate the desired product **73** in 76% yield, when enone **72** is heated with phenylboronic acid in an aqueous dioxane solution at 100°C for 4 hours (Scheme 56). A variety of boronic acids were effectively coupled in this fashion in moderate to high yields. ^1H and ^{13}C NMR revealed the presence of a single anomer for all products, which were assigned the α-configuration by comparison to known products.



Scheme 56

Reetz has performed the enantioselective 1,4-addition on the α-acetamido acrylic acid ester **74**, using chiral bis(phosphinite) ligands.[70] Treatment of **74** with phenylboronic acid in aqueous dioxane with a catalyst prepared from $[Rh(acac)(C_2H_4)_2]$ and ligand **76a**, afforded the protected phenylalanine **75b** with 70% ee. Furthermore, the addition of sodium fluoride to the reaction increased the enatioselectivity to 77% ee, which is of particular interest as it shows that the chiral centre can be created by the enantioselective protonation of the rhodium-enolate at the α-carbon (Scheme 57).



Scheme 57

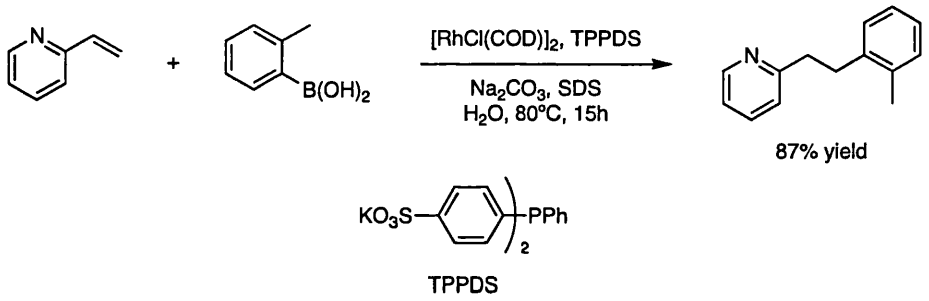
1.3.2 Reactions with Unactivated Alkenes and Alkynes

The addition of carbon functionalities to activated alkenes and alkynes is a significant challenge to the synthetic organic chemist. Perhaps the best known reactions are those based on the palladium catalysed Heck reaction which utilises aryl and alkenyl halides and sulphonates as organic electophiles.[5] Alternatively a net C,H-addition to alkynes can be achieved by the generation of alkenyl organometallics, *via* hydroboration[3] or hydrozincation[88] of alkynes with subsequent cross-coupling with organohalides and

sulphonates in a two step sequence. The ability of rhodium-carbon bonds to undergo protonolysis also allures the use of rhodium-catalysis to this type of chemistry

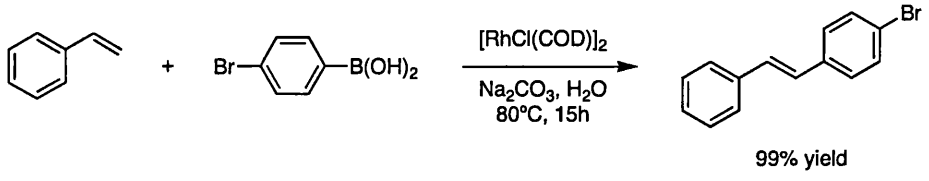
Additions to Alkenes

Lautens[89] and subsequently Genet[60] have reported the addition to heteroaromatic vinyl compounds in aqueous medium (Scheme 58).[89] Lautens primary studies were performed in water with the phase transfer catalyst sodium dodecyl sulfate (SDS), and the water-soluble phosphine ligand TPPDS. Although the addition of SDS was not essential for an efficient reaction, a rate enhancement was observed in its presence. Furthermore a reduction in the rate of protodeborylation was also observed, and hence a lower quantity of boronic acid was required.



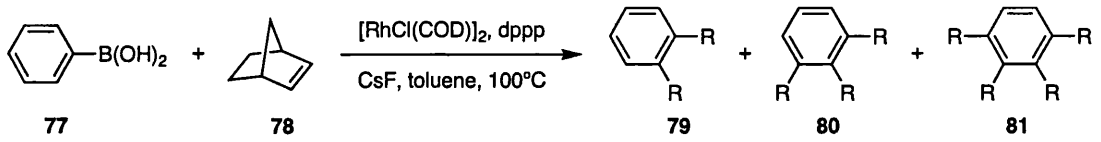
Scheme 58

Interestingly, in the absence of the chelating nitrogen of vinyl pyridines, the reaction of styrene afforded the Heck-type alkene product as the major product (Scheme 59). The olefin is thought to be regenerated through a β-hydride elimination step similar in manner to the palladium catalysed Heck reaction,[5] with an intermediary rhodium hydride species, as a result of the lack of a chelating stabilising group. The Heck-type addition to α,β-unsaturated esters has since been reported by Zou *et al.* however the reaction is highly dependent on steric factors.[90]



Scheme 59

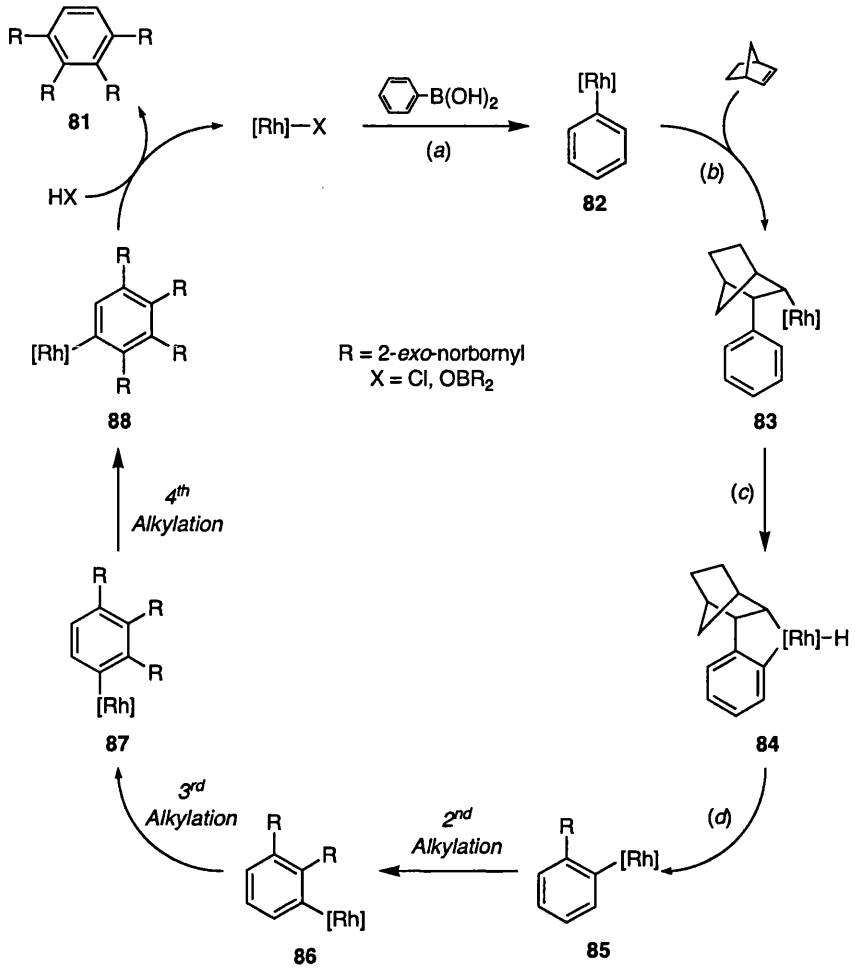
The addition of arylboronic acids to strained alkenes is illustrated by the addition to boronic acids to 2-norbornene as presented by Miura and co-workers whose research was interested in the transition metal catalysed domino or merry-go-round sequential allylations.[91] Initial experiments with 7 equivalents of norbornene **78** to phenylboronic acid **77**, in anhydrous toluene, resulted in the formation of the tetra-substituted 1,2,3,4-tetra(2-norbornyl)-benzene **81**(Scheme 60). It was found that reduction in the amount of norbornene resulted in the increased production of 1,2-di- and 1,2,3-tri-(2-norbornyl)benzenes **79** and **80**.



77 78 79 80 81

Scheme 60

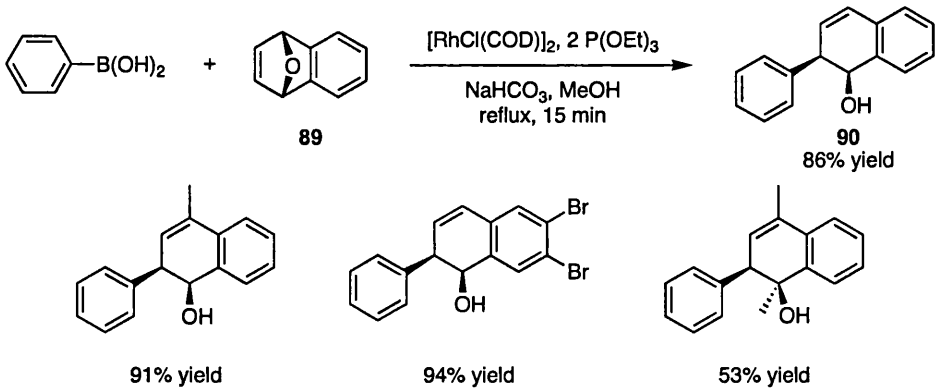
The occurrence of multiple addition reactions is attributed to the absence of water from the reaction. Although the boronic acid can behave as a proton source it is a poor donor for the protonolysis termination step. Through a series of deuterium doped experiments a plausible reaction mechanism was elucidated (Scheme 61). The first step (a) is proposed to be the formation of the arylrhodium species **82** by transmetallation, which is enhanced with CsF. This is followed by coordination and insertion of the alkene into the phenyl-rhodium bond in an *exo* fashion (b), then cyclorhodation *via* C–H cleavage (c) and intramolecular reductive elimination (d) affords **85**. Subsequent insertion-cyclorhodation-reductive elimination process occur three times, or until termination through protonolysis with the boronic acid species, to form the multi-alkylated arene ring. After four additions the steric bulk is proposed to block any further insertions of norbornene.



Scheme 61 Proposed mechanism for the merry-go-round multiple alkylation of aryl boronic acids

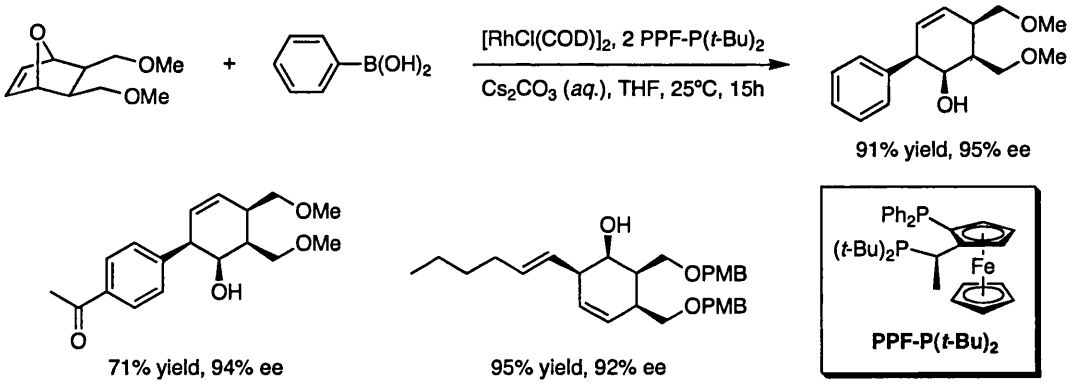
β-Oxygen Eliminations

Murakami and Igawa have demonstrated that aryl and alkenyl boronic acids can be added to oxabenzonorbornadienes **89**, through rhodium catalysis, to generate the oxa-ring opened product **90** (Scheme 62).[49] The use of phosphite ligand $P(OEt)_3$ with $[RhCl(COD)]_2$ and 2 equivalents of $NaHCO_3$ in refluxing methanol, was found to be the most effective conditions. Phosphine ligands, such as PPh_3 or dppp, were found to retard the reaction, with the production of the dehydration product 2-phenylnaphthalene observed as the major product in these cases.



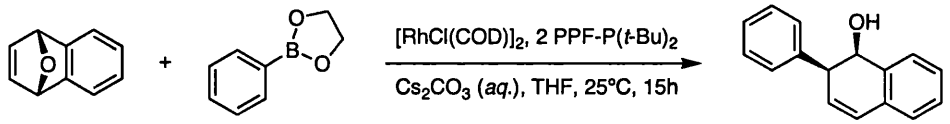
Scheme 62

Lautens has reported the enantioselective β-oxygen elimination reaction, using the chiral ligand PPF-P(*t*-Bu)$_2$ and aqueous cesium carbonate as base.[92] Studies on the addition of arylboronic acids to oxabicyclic alkenes showed that a range of boronic acids were compatible, including vinyl species, with high enantioselectivities achieved for all (Scheme 63).



Scheme 63

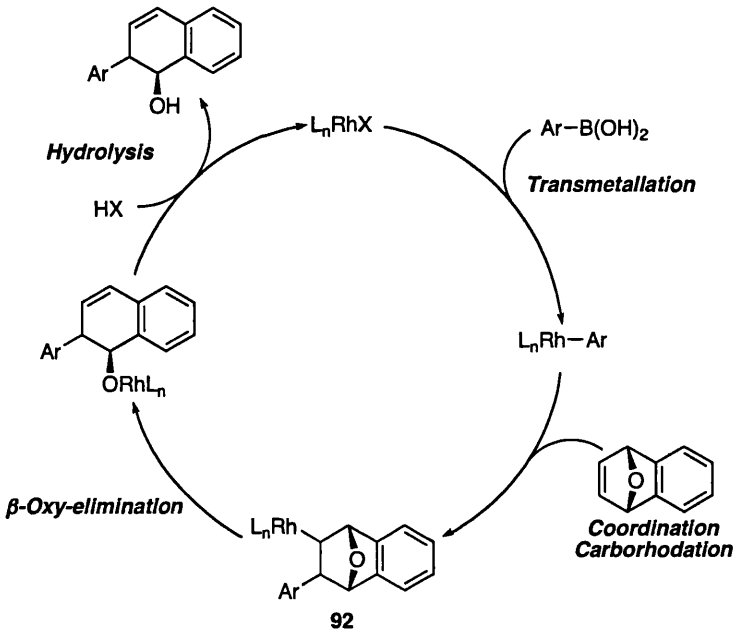
Although the conditions presented by Lautens for the enantioselective β-oxygen elimination reaction were ineffective for the addition of phenyl boronic acid to oxabenzonorbornadiene **89**, exchange of the boronic acids for phenylboronic ethyleneglycol **91**, afforded **90** in 78% yield and 92% ee (Scheme 64).



89 91 90
78% yield, 92% ee

Scheme 64

Murakami and Lautens independently proposed similar mechanisms for the ring opening reaction (Scheme 65). Initial transmetallation of the organoboronic acid to the rhodium is followed by coordination of the alkene with insertion into the Rh–C_{Aryl} bond. Whilst complex **92** closely resembles **83** from Miura's domino reaction (Scheme 61, on page 42), no *ortho* C–H insertion products were observed. Thus β-oxy-elimination exclusively proceeds to open the furyl ring. Protonolysis of the resultant rhodium alkoxide produces the alcohol and regenerates the catalytically active rhodium.

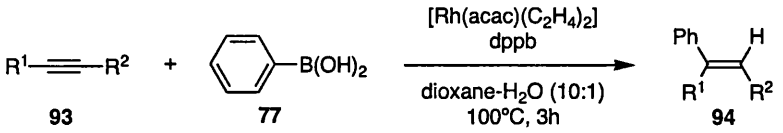


Scheme 65 Proposed mechanism for the β-oxy-elimination reaction

Additions to Alkynes

Hayashi was first to describe the hydroarylation of alkynes to produce trisubstituted alkenes in high yields and isometric purity, with both inactivated and activated alkynes efficiently coupled in high yields.[93] For example, the reaction of 4-octyne **93a** with phenylboronic acid in an aqueous dioxane solution at 100°C with a rhodium catalyst, generated from [Rh(acac)(C_2H_4)$_2$] and dppb, afforded (*E*)-4-phenyl-4-octene **94a** in 95%

yield and 97% isomeric purity. The formation of the (*E*) product is indicative of *syn* addition of the phenyl group and proton to the alkyne (Scheme 66).

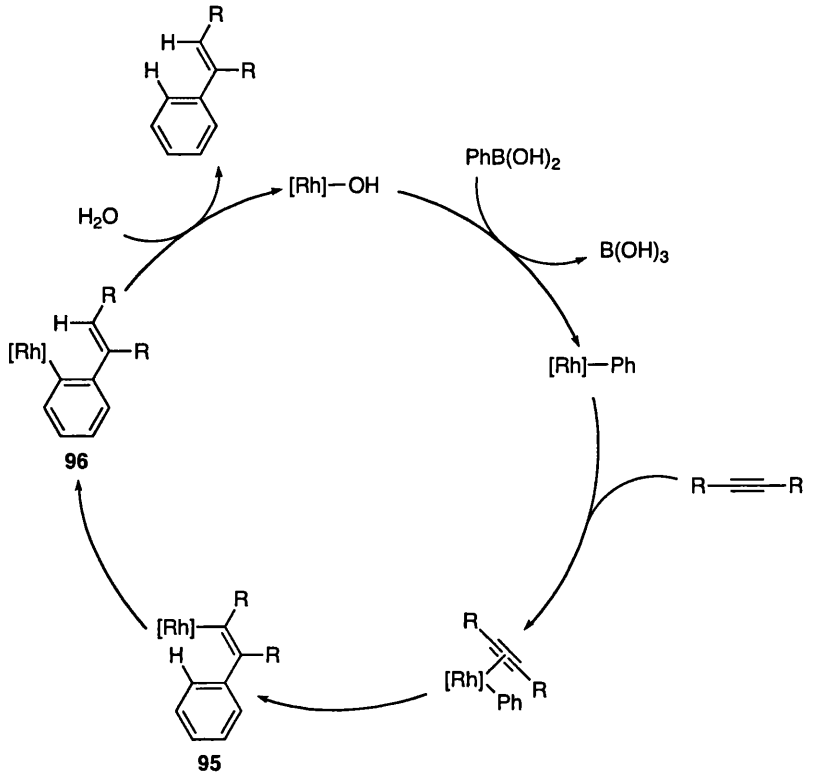


93 77 94

		Product	yield %
93a:	$R^1 = R^2 = n$-Pr	94a	95
93b:	$R^1 = R^2$ = Et	94b	89
93c:	R^1 = Me, R^2 = Ph	94c	96 (3:1 mixture of regioisomers)
93d:	$R^1 = n$-Bu, $R^2 = CO_2Me$	94d	81
93e:	$R^1 = Me_3Si$, $R^2 = CO_2Me$	94e	70
93f:	$R^1 = n$-Hex, $R^2 = P(O)(OEt)_2$	94f	87

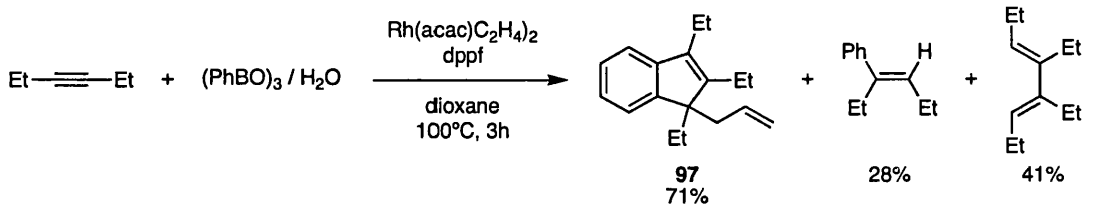
Scheme 66

Addition to acetylenes substituted with electron withdrawing groups, such as esters or phosphonates, proceeds regiospecifically at the β-position, however, in the absence of an activating functionality unsymmetrical alkynes gave mixtures of regioisomers. Interestingly, deuterium experiments showed the reaction of symmetrical alkynes to involve a 1,4-shift of rhodium from 2-aryl-1-alkenylrhodium **95** to 2-alkenyl-arylrhodium **96** (Scheme 67), similar to that observed by Miura[91] (Scheme 61).



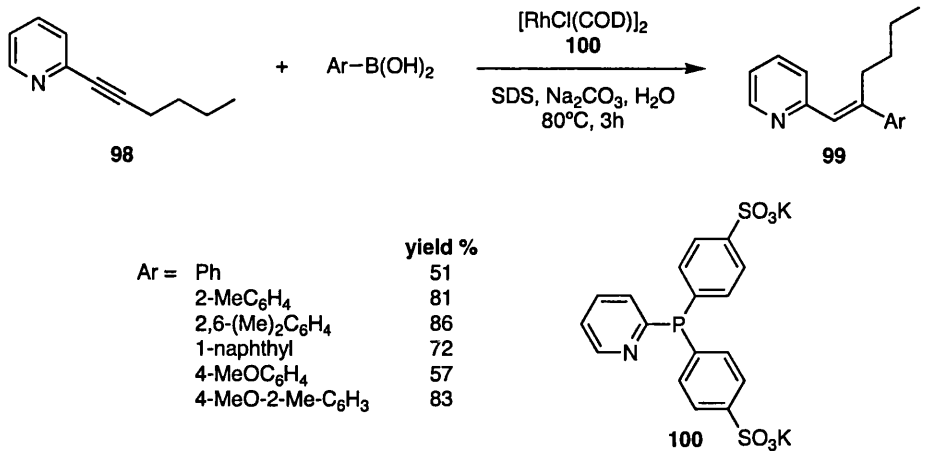
Scheme 67

Although the 2-alkenylarylrhodium species **96** does not add to a further molecule of alkyne under these conditions, the addition does occur when the addition of arylboroxine is performed in the presence of a large excess of alkyne, with a minimum amount of water. Thus the reaction of phenylboroxine with 3-hexyne in the presence of one equivalent of water to boron, gave indene **97** (Scheme 68).



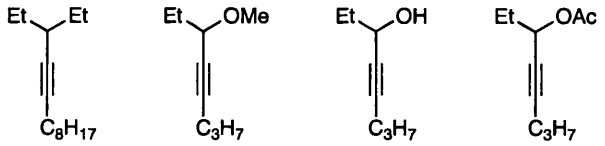
Scheme 68

Subsequent to work previously published *vide supra* (Chapter 1.2.2), Lautens investigated the rhodium catalysed addition of arylboronic acids to alkynylpyridines.[94] The reaction of 2-(1-hexynyl)pyridine **98** with phenylboronic acid, performed in the presence of $[RhCl(COD)]_2$, ligand **100**, Na_2CO_3 and the phase transfer catalyst SDS in water at 80°C for 3 hours, generated the hydroarylation product **99** in 51% yield (Scheme 69). Substitution at the *ortho*-position of phenylboronic acid gave better results, with 2-methylphenylboronic acid generating the desired product in 81% yield. The alkynyl group must be in the two position on the pyridine ring for the reaction to proceed, thus when 2,5-di(pent-1-ynyl)pyridine was reacted with 2-methylphenylboronic acid hydroarylation occurred solely on the *ortho*-positioned alkyne. Hence the reaction is proposed to proceed *via* an alkenylrhodium species stabilised by the chelating *ortho*-nitrogen.

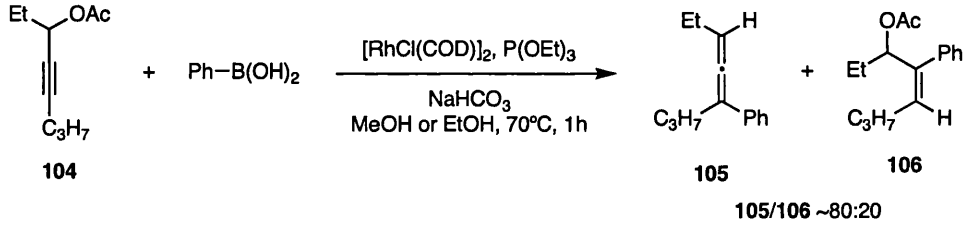


Scheme 69

The addition of aryl boronic acids to unsymmetric acetylenic compounds **101-104** has been investigated by Murakami and Igawa who were interested in β-oxygen elimination within these systems.[95]



Unsymmetrical alkyne **101** with no *O*-functionality afforded a racemic mixture of regioisomers from the hydroarylation reaction. Propargylic methyl ether **102** and alcohol **103** displayed some regioselectivity with ~60:40 and ~80:20 mixtures formed respectively. The dominant products arose from the addition of rhodium to the carbon-atom proximal to the *O*-functionality. Coordination of the oxygen to rhodium was proposed to be responsible for this observed selectivity. The greater leaving group ability of the acetoxy group of **104** over the methoxy or hydroxy groups of **102** and **103** respectively, grants the additional β-*oxy*-elimination step when the acetoxy group is proximal to the rhodium. Thus reaction of phenyl boronic acid with propargylic acetate **104** generates a mixture of the trisubsituted allene **105** (β-*oxy*-elimination) and allylacetate **106** (protonation) products in an 80:20 ratio, with the former dominating (Scheme 70).



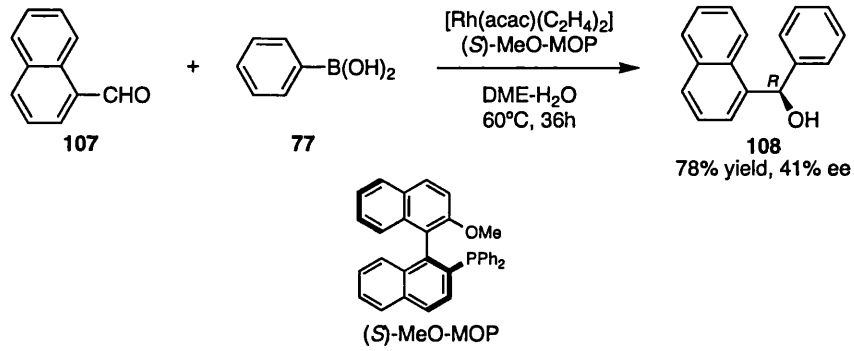
Scheme 70

1.3.3 1,2-Additions to Carbonyls and Imines

The addition of carbon nucleophiles to carbonyl and heterocarbonyl compounds such as ketones, aldehydes and imines, is an important transformation commonly employed in organic synthesis for the production of carbon-carbon bonds. These reactions are exemplified by the Barbier-Grignard type reactions, which proceed in high yields. However, the success of these reactions is dependent upon the protection of sensitive functional groups. Whilst the knowledge of protecting groups has improved dramatically in order to compensate for such chemoselectivity issues, a far more attractive approach would be to utilise nucleophiles that do not suffer from these issues. As highlighted with the rhodium catalysed 1,4-conjugate addition reaction rhodium catalysis of boronic acid additions provide chemists with attractive alternatives to the Grignard-type addition reactions now commonplace in organic synthesis.

Additions to Aldehydes and Ketones

In 1998 Miyaura reported that the combination of $[Rh(acac)(CO)_2]$ and bis-phosphine ligands with large bite angles, effectively catalysed the 1,2-addition of aryl and alkenyl boronic acids to aryl aldehydes.[96] The reaction was found to be sensitive to electronic effects on both the aldehyde and boronic acid. Indicative of a mechanism involving nucleophilic attack of the aryl group on the aldehyde, the reaction was accelerated by the presence of electron withdrawing groups on the aldehyde and electron donating on the boronic acid. The asymmetric addition was also achieved by the use of (*S*)-MeO-MOP as a ligand. Treatment of phenylboronic acid **77** and 1-naphthaldehyde **107** with $[Rh(acac)(C_2H_4)_2]$ and (*S*)-MeO-MOP in aqueous DME at 60°C, generated the desired secondary alcohol **108** in 78% yield and 41% ee, with (*R*)-selectivity (Scheme 71). Surprisingly, unlike for the 1,4-addition, the use of DIOP and BINAP gave only the racemic product.

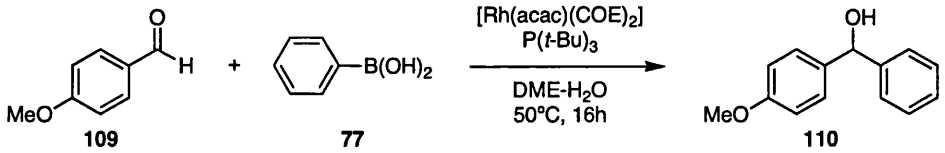


107 **77** **108**
78% yield, 41% ee

(*S*)-MeO-MOP

Scheme 71

Miyaura later reported that large accelerating effects were evident when bulky, electron donating alkyl mono phosphines were applied to the reaction, with tri(*tert*-butyl)phosphine found to be the most active ligand when combined with $[Rh(acac)(COE)_2]$.[97] The addition of phenylboronic acid **77** to 4-methoxybenzaldehyde **109** could be performed, in aqueous dioxane or DME solutions at room temperature, quantitatively yielding the desired alcohol **110**. Interestingly, the stoichiometry of the ligand to rhodium is significant, with the reaction accelerated most by a 1:1 ratio and slowed considerably by the use of excess mono-phosphine (Scheme 72). Unlike the previously reported reactions with bis-phosphines, no electronic effects were observed for the alkyl mono-phosphines. Aliphatic aldehydes could also be coupled, however the reactions were slow at room temperature; a factor attributed to the lower electrophilicity when compared to the corresponding aryl-aldehydes.



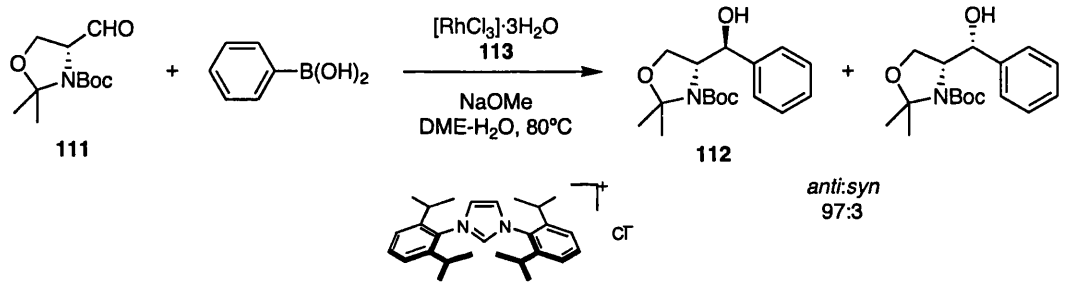
109 **77** **110**

P(*t*-Bu)$_3$ (equiv. to Rh)	yield %
1	99
2	67
3	57

Scheme 72

Carbene ligands also express activity in the 1,2-addition reaction to aldehydes.[98] Imidazolium salts possessing bulky *N*-aryl groups displayed the highest levels of activity with *N*-alkyl groups tending to be less efficient. Optimised conditions were

determined to be the reaction of aldehyde with 2 equivalents of the boronic acid and a catalyst generated in situ from the imidazolium salt **113** and $[RhCl_3]\cdot 3H_2O$ with NaOMe in an aqueous DME solution, heated to 80°C for 30 minutes. Addition reactions to the Garner aldehyde **111** provided a high selectivity for the *anti*-configured alcohol **112** (Scheme 73). This selectivity is likely to originate from a non-chelation controlled pathway, caused by the low affinity of the electron-rich rhodium center to the *hard* donor sites in **111**.

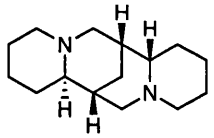


111 112 anti:syn 97:3

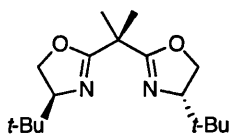
113

Scheme 73

Frost *et al.* have highlighted the importance of the rhodium complex counterion on the activity displayed by influencing the Lewis acidity of the rhodium centre.[99] Results indicated the rate of reaction raises with increasing Lewis acidity of the metal centre. Thus the best results were obtained with weakly coordinating anions such as carboranes ($CB_{11}H_{12}^-$). During their studies Frost and co-workers recognised the applicability of (-)-sparteine **114** and bisoxazalines **115** as efficient ligands for the 1,2-addition to aldehydes.

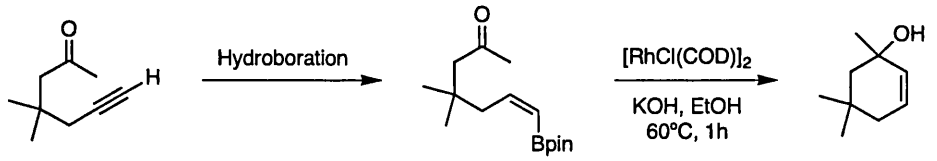


114



115

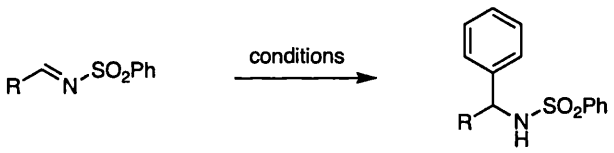
Other borane sources can be used for the addition to aldehydes including potassium trifluoroborate salts[73] and boronic esters,[100] often showing increased reactivity over their boronic acid equivalents. The addition of 1-alkenylboronic acids and esters to aldehydes and ketones has been highlighted by Miyaura as a facile method for the formation of five and six membered cyclic alkenes from alkynyl ketones (Scheme 74).



Scheme 74

Additions to Imines

The analogous 1,2-addition to *N*-sulfonyl aldimines has also been reported.[101,102] Although initial experiments with boronic acids failed to give the desired amine, due to hydrolysis of the imine to the aldehyde with subsequent 1,2-addition to form the alcohol as above. Tetraphenyl borate was a viable substitute for boronic acids, with all four phenyl groups transferred from the borane to the aldimines, using the cationic rhodium salt $[Rh(COD)(MeCN)_2][BF_4]$ and dppb as ligand.[101] It was later reported that the reaction could be performed with boronic acids and esters in the absence of water. However the addition of base was required for the smooth coupling of boronic esters (Scheme 75).[102] Interestingly the use of $[Rh(acac)(COE)_2]$ with $P(i\text{-}Pr)_3$, enables the selective addition to α,β-unsaturated aldimines in a 1,2-fashion in preference to the 1,4-addition.



Conditions: 1. a) $[Rh(COD)(MeCN)][BF_4]$, dppb, Ph_4BNa, dioxane, 90°C, 3-16h; b) H_2O

2. a) $[Rh(COD)(MeCN)][BF_4]$, $PhB(OR)_2$, Et_3N, dioxane, 95°C, 16h; b) H_2O

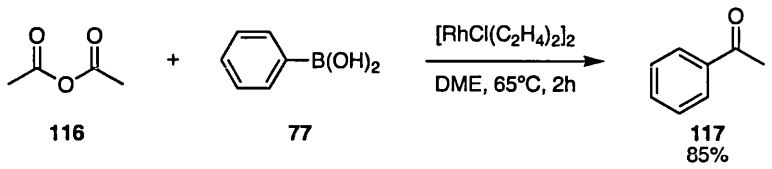
Scheme 75

1.3.4 Further Rhodium-Catalysed Coupling Reactions with Organoboranes

Ketone Formation

Frost and Wadsworth have demonstrated the Friedel-Crafts like acylation reaction of arylboronic acids with acid anhydrides, as a method for the formation of aryl ketones.[103] For example heating phenylboronic acid **77** with acetic anhydride **116** in the presence of

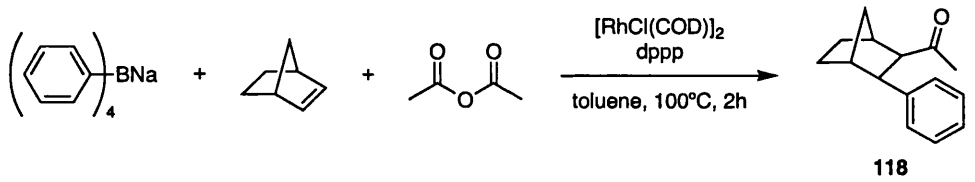
$[RhCl(C_2H_4)_2]_2$ in either DME or a DME-water mix, generated benzophenone **117** in 85% yield (Scheme 76). A range of boronic acids can be coupled including electron rich and electron deficient arenes and alkenes. The successful coupling of deactivated aryl derivatives compliments the reactions already possible by Lewis acid catalysis.



116 **77** **117** 85%

Scheme 76

Miura has reported a similar reaction coupling tetra-aryl borates with acid anhydrides.[104] Unlike the work reported by Frost, phosphine ligands were found to be beneficial to the reaction. Application of this work enabled the inhibition of the merry-go-round addition reaction observed by Miura[91] *vide supra* (Chapter 1.3.2) by the reaction of alkyl rhodium species **87** (Scheme 61, on page 42) with acetic anhydride to form *exo*-2-acyl-*exo*-3-phenylbicyclo[2.2.1]heptane **118** (Scheme 77).



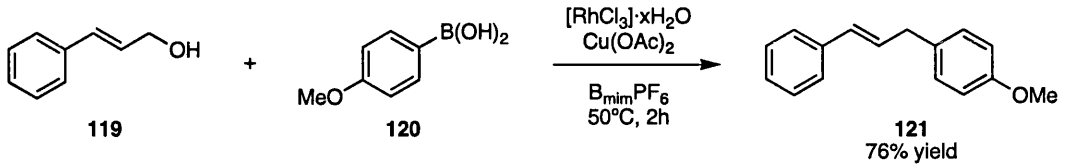
118

Scheme 77

Allylation Reactions

Kabalka has recently reported the direct allylation of cinnamyl alcohols using boronic acids, catalysed by ligandless rhodium complexes.[105] For example the coupling of cinnamyl alcohol **119** with 4-methoxyphenyl boronic acid **120**, by $[RhCl_3]\cdot xH_2O$ and $Cu(OAc)_2$ in the ionic liquid 1-butyl-3-methylimidazolium hexafluorophosphate ($B_{mim}PF_6$) generated the allylphenyl **121** in 76% yield (Scheme 78). Although the copper salts presence was not required for a successful reaction, a slight increase in yield was observed by its presence. Electron-rich boronic acids were found to generate products in higher yields than electron-deficient, with *ortho*- and *meta*-substituted arylboronic acids typically affording lower yields than *para*-substituted ones. Due to the use of the ionic

liquid the catalyst can be recycled with no significant loss in activity. Although a detailed mechanistic study has not been performed the authors propose that rhodium oxidatively adds into the C-O bond of the cinnamyl alcohol forming a π-allyrhodium system, which subsequently undergoes transmetallation with the boronic acid. Reductive elimination from the aryl-rhodium-allyl species forms the desired product, regenerating the active catalyst.



119 + **120** → **121** 76% yield

Scheme 78

CHAPTER TWO:

Design and Synthesis of Novel Sulphone Containing Ligands

2 Design and Synthesis of Novel Sulphone Containing Ligands

2.1 Aims and Objectives

The objective of this project was to design and synthesise novel hybrid ligands and catalysts, from readily available starting materials. Ultimately these ligands should display high activity in a range of transition metal catalysed reactions involving arylhalides and arylboronic acids.

2.2 Envisaged Programme of Work

Initial studies would concentrate on the design of modular achiral hybrid ligands, allowing for the inclusion of chiral functionalities at a later time. Synthesis of the ligands and transition metal complexes would follow, with efforts made to show the complex with both the substitutionally labile moiety bound, and unbound, to the metal centre. Activity of the ligands in transition metal catalysis shall be investigated through the application of the ligands to the palladium catalysed Suzuki-Miyaura cross-coupling. The coupling of 4-bromo- and 4-chloro-toluene with phenylboronic acid would be attempted using conditions previously published by Nolan and co-workers.[106] Further studies assessing additional boronic acids would be attempted, together with the coupling to different aryl chlorides, should the ligands prove to be active.

2.3 Background

Transition metal catalysed reactions have become an integral tool in the synthesis of many biologically interesting and synthetically challenging molecules. However, the diversity of reactions catalysed and mediated by metals is not only a function of the metals themselves, but also the ligands which bind to them.

The use of transition metal catalysts in organic transformations is well documented,[107] with the ability to undertake reactions catalytically bringing both economical and

environmental advantages; reducing the need for high temperatures, long reaction times and large quantities of often harmful reagents.

Over recent years there has been a lot of research into the chemistry of ligands and the advantages they bring to synthetic chemistry, through their use in reactions catalysed by transition metal complexes. We can define the term *ligand* as "*any molecule or ion that possesses the ability to donate at least one pair of electrons*". Also electrons can often be accepted from the metal into vacant orbitals with appropriate symmetry, termed *back bonding*.[108] Ligands are nucleophiles and as such can be termed Lewis bases, in accordance with the acid base definition as stated by Lewis.[109] Metal ions or molecules, such as BF_3, having incomplete valence electron shells are electrophiles or Lewis acids.

In recent years the chemistry of a class of ligands, containing two or more functionalities, combining both soft and hard donors in the same ligand, has received particular attention.[110,111] The expectation is that the contrasting chemistries can be associated within the same molecule, leading to novel properties for the resultant metal complex. These ligands have a range of names, the most common being: hybrid, heteroditopic and hemilabile ligands. Jeffery and Rauchfuss first introduced the term "*hemilabile ligand*" in 1979.[112] However, earlier examples of bifunctional ligands containing mixed bonding characteristics can be found in the literature.[111] Subsequently, a broad range of ligands, with coordinating groups differing in activity, have been synthesised and complexed to various metal centres. All these studies share the same basic characteristics of hemilabile ligands, as illustrated in Figure 1:

- The ligands are polydentate chelates, containing at least two different types of chemical functionality (denoted α and β in this chapter) capable of binding to metal centres.

- One group, α, binds strongly to the metal centre (*substitutionally inert*) whilst β binds weakly (*substitutionally labile*). β can be easily displaced by coordination of ligands or solvent molecules υ. In this way, β can be displaced from the metal centre, yet remains available for re-coordination; consequently this can be a reversible reaction.

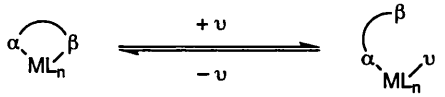


Figure 1

It should be noted that often when the term hybrid ligand is used it is not assumed that one moiety dissociates from the metal centre although it is highly likely that this occurs in many systems.

Hemilabile ligands have been designed in many forms with group α taking a number of different guises, including: carbon, nitrogen, arsenic, chalcogens and the most common; phosphorus. The transition metal chemistry of hemilabile ligands has been presented in some comprehensive review articles.[109-111,113] Although such aspects will not be discussed in detail herein, it is perhaps interesting to note that hemilability is not restricted to man made systems. Protein backbones in bioinorganic protein-metal complexes display behaviour analogous to designed hemilabile ligands. For example, metalloenzymes, such as the matrix metalloprotease, human fibroblast collagenase utilises a hemilabile mechanism in its activation.[114] The active site of the protein contains a zinc ion bound in a protein pocket. When the protein is in an inactive state the zinc ion is masked by the protein backbone *via* the coordination of a cysteine residue. The metalloenzyme can be switched from this inactive to an active form by dissociation of the zinc cysteine bond, with the subsequent binding of water to the now vacant coordination site (Figure 2).

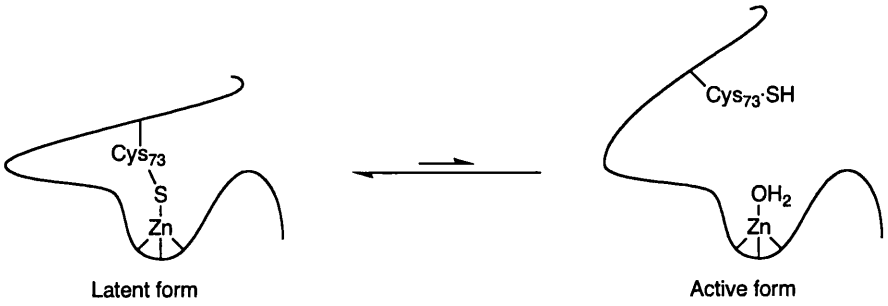
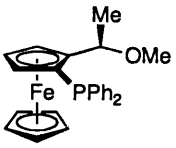


Figure 2 The activation/deactivation of collagenase *via* coordination to cysteine$_{73}$

Incentives to study hybrid ligands are diverse; hemilabile ligands can stabilise reactive transition metal complexes and endow the possibility of open coordination sites

throughout the course of the reaction, which are *masked* in the ground-state structure. Thus, transition metal complexes containing hemilabile ligands have been utilised in a range of reactions including: Heck;[115] hydrogenation;[116] amination;[117] Suzuki;[118] hydroborations,[119] and conjugate additions.[120]



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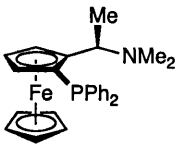

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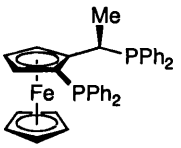

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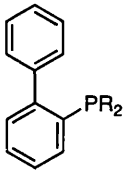
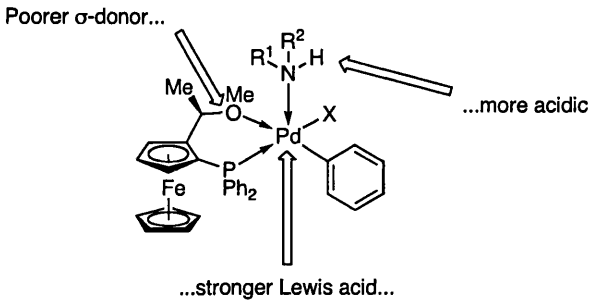


125a R = Cy
125b R = *t*-Bu

In 1998 Buchwald published results on the palladium catalysed amination reaction using the hybrid ligands **122-124**.[121] It was observed that the catalytic activity increased with the decreasing σ-donor capacity of the labile group: $-PPh_2$ > $-NMe_2$ > -OMe. However, the rationale for the increased activity for the weaker σ-donating, -OMe, was not the dissociation of the oxygen ligand from the palladium centre, but rather, the oxygen remained bound. The decreased σ-donating capability of the ether oxygen over phosphorus and nitrogen, implied that the Pd(II) centre in the intermediate **126** (Figure 3) was more Lewis acidic and hence would bind the amine more tightly, which in turn weakens the N-H bond making the amine bound proton more acidic. Buchwald's group have since produced a range of hybrid ligands for application in the amination of aryl halides, including ligands such as **125a** and **125b** which are postulated to act as π-donors from the *ortho*-phenyl group with η^2 bonding characteristics.[122]

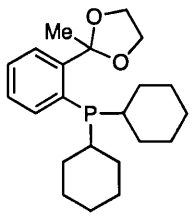


126

Figure 3

During the course of 1999 Guram's group published a number of results presenting the high activity of 2-(2'-dicyclohexylphosphinophenyl)-2-methyl-1,3-dioxolane **127**, as a

hemilabile ligand, in the catalysis of Suzuki and amination reactions with aryl halides including chlorides.[118,123,124] Single crystal X-ray diffraction studies confirmed the coordination of one of the dioxolane oxygens to the palladium centre.



127

2.4 LIGAND DESIGN AND SYNTHESIS

Over recent years there has been a great deal of literature published on the design and synthesis of ligands for transition metal-catalysed reactions, with a large number of functional groups applied to coordinate to the metal centre, either in a substitutionally-inert or -labile manner. Using Buchwald's rationale, that for increased reactivity one can use hybrid ligands,[121] studies focused on finding atoms or groups that when used in conjunction with a phosphine moiety would supply the necessary properties, both stereochemical and electrochemical, to enhance the activity of palladium in reactions such as the coupling of α-amino acids with aryl halides.

The use of oxygen as a hemilabile function in ligands has been the object of much research, due to the poor σ-donating properties of oxygen. However, although previous applications have utilised the oxygen in most forms, including: amides, ethers and ketones, the use of sulphone oxygen as a coordinating moiety has yet to be investigated in any real depth (Figure 4).

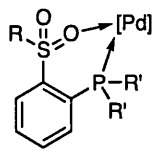
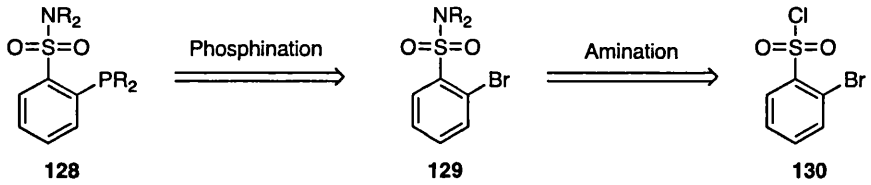


Figure 4 predicted binding of phosphorus sulphone to a palladium centre

2.4.1 Sulphonamide Ligands

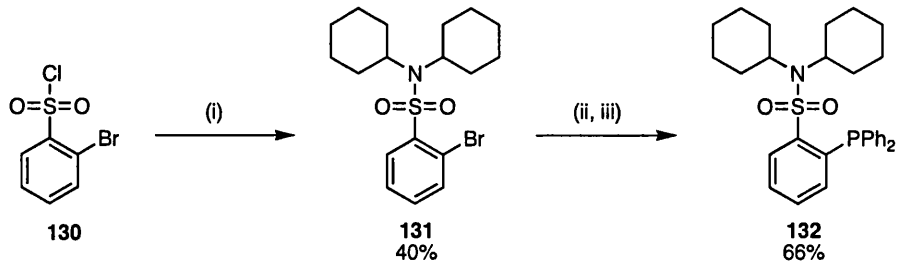
Initial studies concerned with the application of sulphone oxygens as hemilabile moieties centred on the structure of an arylsulphonamide, with an adjacent phosphine group, **128**. Although the sulphonamide was predicted to bind through an oxygen, coordination through the *tertiary* nitrogen could not be ignored as a possibility, as shown by Hiroi *et al.*[125] Retrosynthesis of **128** to commercially available starting materials was achieved in two steps (Scheme 79). The first disconnection involves the phosphination of aryl bromide **129**, and the second a coupling of a sulphonylchloride with an amine. 2-Bromo-benzenesulphonyl chloride **130** was envisaged to be a suitable starting point, enabling the phosphination step to be confidently performed, *via* lithiation of the aryl halide, *ortho* to the sulphonamide.



128 **129** **130**

Scheme 79

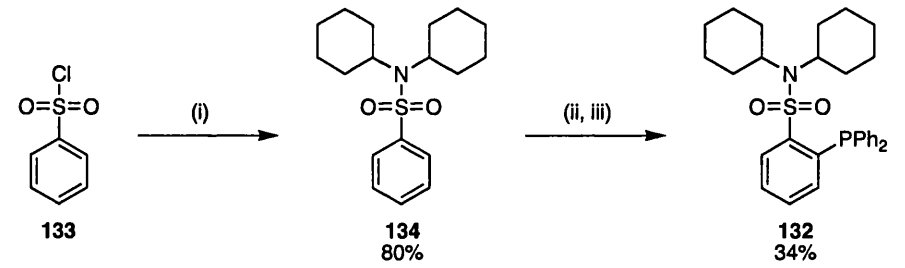
The synthesis of 2-bromo-*N,N*-dicyclohexyl-benzenesulphonamide **131** (Scheme 80), was accomplished by the DMAP mediated coupling of **130** with dicyclohexylamine, at reflux for 5 hours, in a disappointing 40% yield. Lithiation of **131** with *n*-BuLi and subsequent quenching of the lithium salt with chlorodiphenylphosphine, gave a crude mixture containing the desired product **132** with traces of both **131** and the reduced arene sulphonamide **134**. Removal of these impurities was realized through flash chromatography to afford analytically pure *N,N*-dicyclohexyl-2-(diphenyl-phosphanyl)-benzenesulphonamide **132** in 66% yield, 26% over the two steps. Although the synthesis is short and widely applicable to a number of amines and chlorophosphines, the high cost of the starting sulphonylchloride was a major disadvantage of an otherwise good synthesis.



130 131 40% 132 66%

Scheme 80 Synthesis of *N,N*-dicyclohexyl-2-(diphenyl-phosphanyl)-benzenesulphonamide **132**, (i) dicyclohexylamine, DCM, DMAP, Et_3N; (ii) *n*-BuLi, -78°C; (iii) $ClPPh_2$

A number of publications have investigated the *ortho*-lithiation of sulphonamides, as recently reviewed by Familoni,[126] indicating that aryl sulphonamides like aryl ethers are *ortho* directing. This precedent encouraged the synthesis of **132** using the much cheaper benzenesulphonyl chloride[127] **133**, as the starting material. Initial attempts to couple **133** with dicyclohexylamine using 4-(*N,N*-dimethylamino)pyridine (DMAP) in refluxing dichloromethane led to a disappointing 35% yield. However, the direct reaction of **133** with an excess of dicyclohexylamine in dichloromethane at ambient temperature afforded the same product in a more respectable 83%. Disappointingly, the phosphination of **134** with chlorodiphenylphosphine to afford **132** was achieved in 34% yield, significantly lower than that obtained from bromide **131**. Thus, with an overall yield of 27%, the modified synthetic route is not ideal, it does, however, offer substantial economic benefits over the previous methodology.

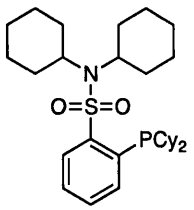


133 134 80% 132 34%

Scheme 81 Modified synthesis of **132**, (i) dicyclohexylamine (4 equiv.), DCM; (ii) *n*-BuLi, THF, -78°C; (iii) $ClPPh_2$

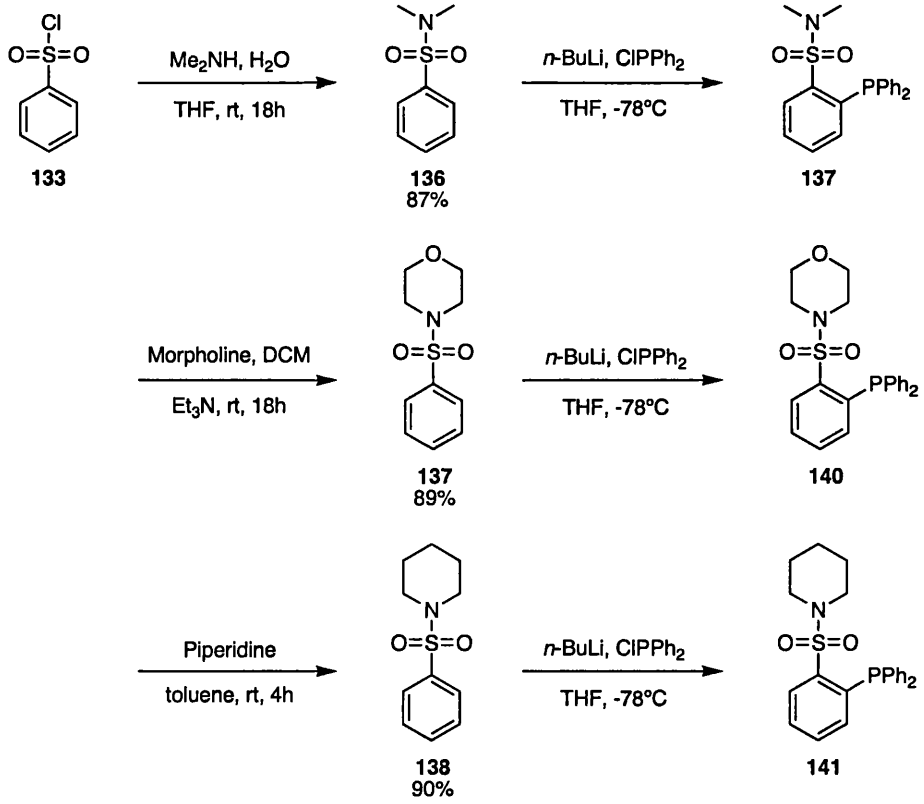
Research has shown that the basicity of the phosphine in ligands has a significant affect on the activity of any complex synthesised, by directly affecting the electronics of the metal centre. It has often been reported that the more basic alkylphosphines possess a higher catalytic activity when applied to palladium-catalysed reactions. To this end the synthesis of the more basic *N,N*-dicyclohexyl-2-(dicyclohexyl-phosphanyl)-

benzenesulphonamide **135** was performed. Interestingly, the phosphination of **134** proceeded in significantly higher yield with chlorodicyclohexylphosphine than previously observed with chlorodiphenylphosphine; 73% and 34% respectively.



135

The amine moiety of the sulphonamide was also proposed to affect the kinetics of a transition metal-catalysed reaction through changes in both sterics and electronics. For example a bulkier group may enhance the rate of reductive elimination by effectively expelling the products from the metal centre, whereas a smaller group might enhance oxidative addition or transmetallation steps.

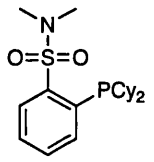


133 **136** 87% **137** **137** 89% **140** **138** 90% **141**

Scheme 82 Synthesis of sulphonamide ligands

Three benzene sulphonamides were synthesised: *N,N*-dimethyl[128] **136**, morpholine **137** and piperidine[129] **138**, in high yields (Scheme 82). However, purification of the phosphination products proved to be difficult, with the desired products co-eluting with the benzenesulphonamides.

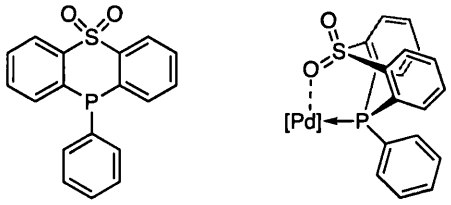
Although the synthesis of diphenylphosphanes proved problematic, *N,N*-dimethyl-2-(dicyclohexyl-phosphanyl)benzenesulphonamide **142** was prepared cleanly in 65% overall yield from benzenesulphonylchloride **133**.



142

2.4.2 Sulphone Ligands

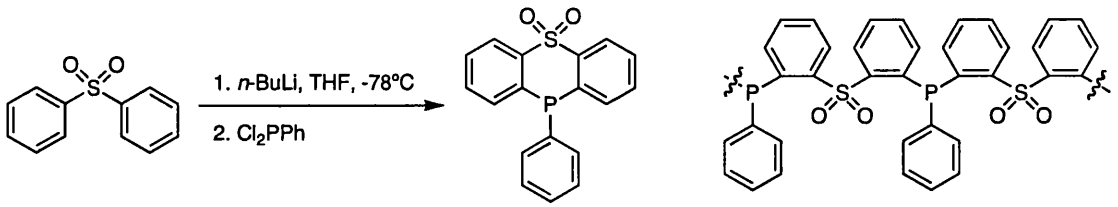
The simple sulphone was also considered to be an important group of ligands, as a direct analogue to the sulphonamides. In the absence of an amine function the ligand should behave in a bidentate fashion through the sulphone oxygen. The most elegant design was that of 10-phenyl-10*H*-9-thia-10-phospha-anthracene-9,9-dioxide, **143**. The six-membered [1,4]-thiaphosphine ring was predicted to sit in a boat formation with the anthracene's terminal phenyl groups pinned back, and together with the phenyl phosphine, the final structure was expected to resemble a crested bird in flight. Predicted to *perch* on the metal centre, binding through the phosphine, a sulphone oxygen remains proximal to the metal centre at all times, to provide a stabilising effect for reaction intermediates by coordinating when required (Figure 5). The oxygen is predicted to be hemilabile and thus rotation around the P-[M] bond is expected to occur.



143

Figure 5

The synthesis of **143**, was proposed from diphenylsulphone **144** *via* a double lithiation, then quenching with dichlorophenylphosphine Cl_2PPh (Scheme 83). Several problems were envisaged with the synthesis, including the formation of the phosphine bridged diphenylsulphone polymer **145**. However, it was anticipated that a high dilution during the phosphination step would enhance the proportion of cyclic monomer over the polymer.



144 143 145

Scheme 83

The phosphination was performed by the double lithiation of diphenylsulphone, 0.15 M in THF, with *n*-BuLi (2.5M in hexanes) followed by the addition of a 0.25 M solution of Cl_2PPh in THF. Gratifyingly, only the desired product was observed in a mixture with unreacted starting material. Purification of the desired ligand was achieved in 67% yield by flash column chromatography. Increasing the concentration of the cyclisation reaction, [diphenylsulphone] from 0.15 M to 0.23 M and [Cl_2PPh] from 0.25 M to 1M, led to a reduction in yield to ~50%, however, none of the polymer was isolated.

Single crystal X-ray analysis of **143** clearly shows the boat formation of the 6-membered [1,4]-thiaphosphine-1,1-dioxide ring (Figure 6). Selected intermolecular distances and angles are presented in Table A - 1(Appendix 1).

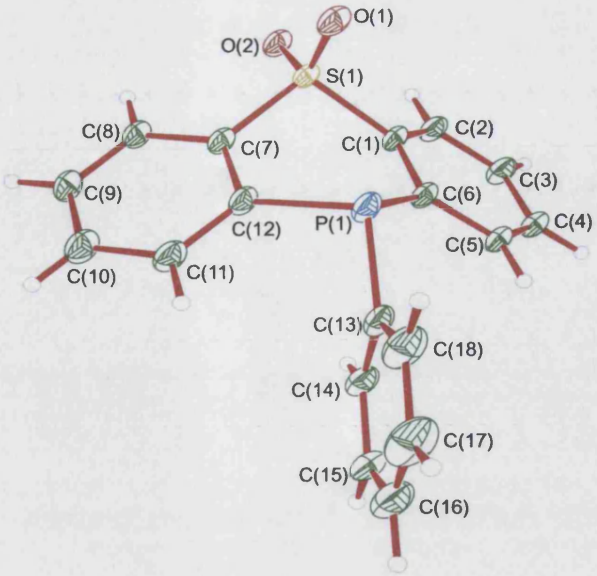
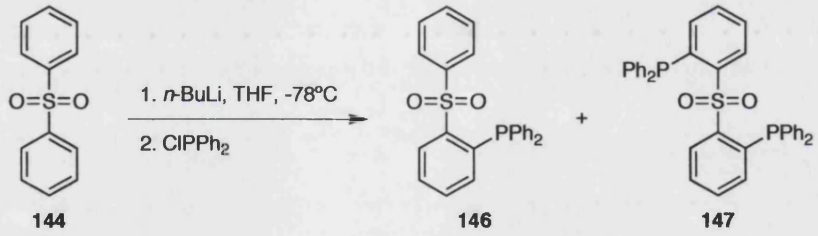


Figure 6 ORTEP plot of the molecular structure of ligand **143**

Additionally, sulphone ligand **146** was synthesised by the reaction of **144** with chlorodiphenylphosphine (Scheme 84). **146** was believed to possess similar properties to **143**, however, the rigid conformation directing the sulphone oxygen toward the metal is no longer present. The formation of bisphosphinated product **147** was observed in low yield during the synthesis of **146**.



144 **146** **147**

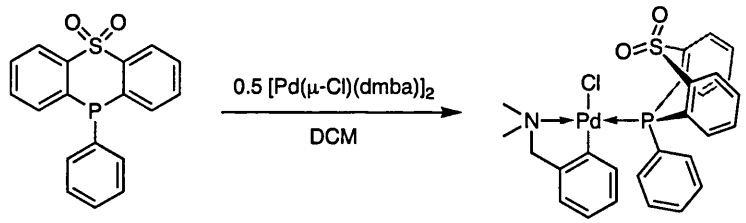
Scheme 84

Ligands **143** and **146** are effectively triphenylphosphine, with an additional sulphone group, which has limited use in the palladium catalysed amination reaction where complexes of triphenyl phosphine afford low yields.[130-132]

2.5 PREPARATION AND STUDIES OF TRANSITION METAL-LIGAND COMPLEXES

Palladium Complexes

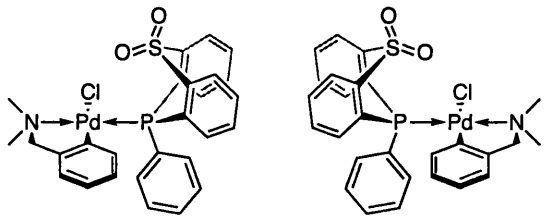
To investigate the possible binding modes of ligands **143** and **132**, palladium complexes were prepared in a similar fashion to that used by Braunstein *et al.*, to show hemilability of acetamide-derived *P,O* phosphine ligands.[133] Reaction of $[Pd(\mu\text{-}Cl)(dmba)]_2$ (dmba-H = *N,N*-dimethylbenzylamine) with 2 molar equivalent of **143** afforded [PdCl(dmba)(**143**)] **147** as a pale green solid.



143 **147**

Scheme 85 Preparation of palladium complex **147**

$^{31}P\{^{1}H\}$ NMR spectroscopy at ambient temperature showed the presence of a single sharp peak at δ 16.43, indicative of a single form in the solution phase. However single-crystal X-ray crystallography showed the presence of two configurational enatiomers, **147a** and **147b** (Figure 7), of the complex each having two distinct conformers (Figure 8).



147a **147b**

Figure 7 Configurational enantiomers of complex **147**

The conformers vary in the amount of tilt of the ligand with respect to the plane of the palladium geometry, thus resulting in a significant variation in the Pd-O interatomic distance, 3.768(2) and 3.407(2)Å (a selection of intermolecular distances and angles are

presented in Table A - 1 (Appendix 1)). The occurrence of two conformers is proposed to be due to packing constraints within the crystal itself. Should the sulphone oxygen bind to the palladium centre in the absence of the chloride ion the tilting observed in the crystal structure, about the P-Pd bond, would be essential for this interaction to occur. The position of the sulphone above the palladium centre is due to steric considerations. Although it is believed that an interaction could occur at this fifth coordinate site, no significant coordination between the palladium and oxygen is observed, with the interatomic distance observed greater than the sum of the covalent radii of palladium and oxygen. The lack of significant variation in the S-O bond lengths is also suggestive of no Pd-O interaction.[134]

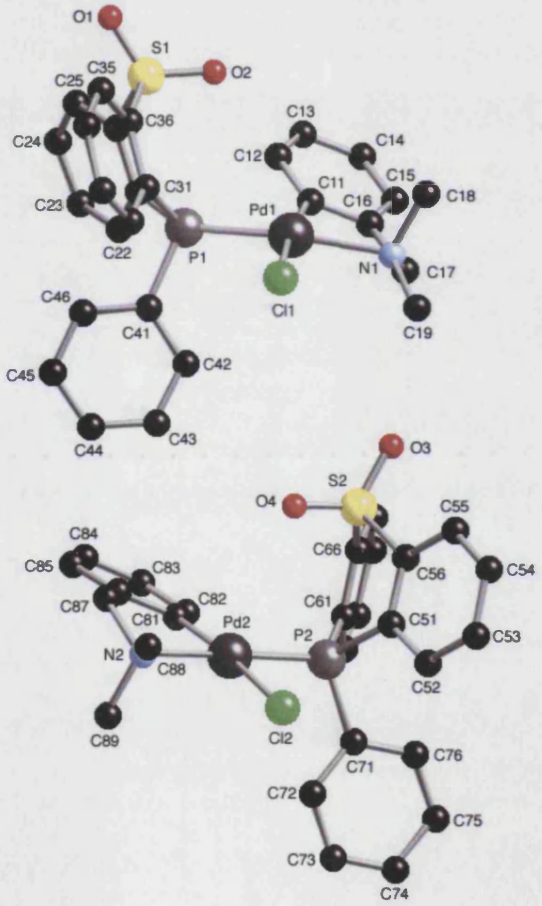
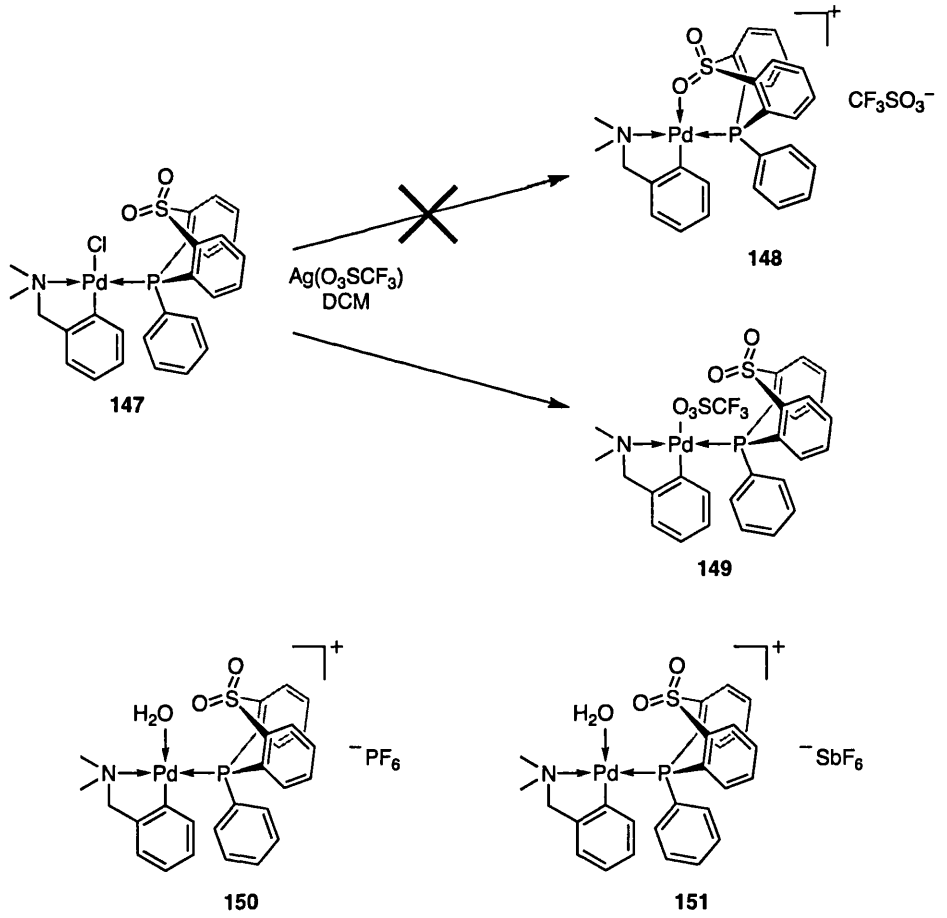


Figure 8 Molecular structure of complex **147**, showing the two configurational isomers and conformers observed in the crystal structure (hydrogen atoms have been omitted for clarity)

Exchange of the chloride ions with other counter ions by treatment of **147** with silver salts was expected to yield cationic Pd^{II} salts with the sulphone oxygen bound to the

palladium such as **148**. Three counterion complexes were prepared: $^{-}$OTf **149**, $^{-}PF_6$ **150** and $^{-}SbF_6$ **151** (Scheme 86), Selected ^1H and $^{31}P\{^1H\}$ NMR data are presented in Table 2, with selected intramolecular distances and angles for **149** (Figure 9) and **151** (Figure 10) presented in Table A - 1 (Appendix 1). Interestingly, a reverse trend was observed in the $^{31}P\{^1H\}$ NMR data to that expected, with a general shift up-field as the Lewis acidity of the palladium increased, with weaker coordinating anions. ^1H NMR spectroscopy of complexes **150** and **151** indicated the presence of water in the complexes, indeed single crystal X-ray analysis of **151** elucidated the structure presented in Scheme 86, with water coordinated in place of the chloride ion of **147**. Although single crystal X-ray diffraction data was not collected for complex **150** the presence of water coordinated to the palladium centre is assumed due to the presence of a signal in the ^1H NMR for water and the correlation between the data collected for **150** and **151.**



Scheme 86 Preparation of palladium complexes **149-151** to investigate possible coodination through the sulphone oxygen

Table 2 Seleced NMR data for ligand **143** and complexes **147**, **149**, **150** and **151**

Complex	Ligand	Salt	^{1}H NMR	^{31}P{^{1}H} NMR
	143			-17.27
147	**143**	Cl^-	2.82 (6H, d, $^4J_{PH}$ = 2.6, $N(CH_3)_2$) 4.05 (2H, d, $^4J_{PH}$ = 2.0, CH_2)	16.43
149	**143**	$CF_3SO_3^-$	2.74 (6H, d, $^4J_{PH}$ = 2.9, $N(CH_3)_2$) 3.95 (2H, d, $^4J_{PH}$ = 1.9, CH_2)	13.29
150	**143**	PF_6^-	2.70 (6H, d, $^4J_{PH}$ = 2.8, $N(CH_3)_2$) 4.01 (2H, d, $^4J_{PH}$ = 2.0, CH_2)	13.47 -142.82 (septet J_{PF} = 1320, PF_6)
151	**143**	SbF_6^-	2.72 (6H, d, $^4J_{PH}$ = 2.8, $N(CH_3)_2$) 4.03 (2H, d, $^4J_{PH}$ = 2.0, CH_2)	12.82

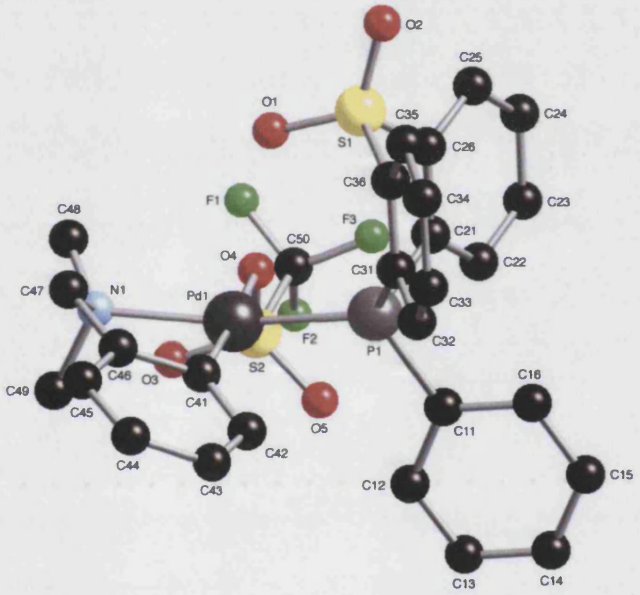


Figure 9 Molecular structure of complex **149** (hydrogens have been omitted for clarity)

Comparison of the data from the X-ray diffraction of complexes **147**, **149** and **151** highlighted a significant shift of the proximal sulphone oxygen toward the palladium centre for weaker coordinating anions: (Pd-O) 3.407(2) – 3.1200(14) – 2.9454(12)Å. However, the lack of an increase in the S-O bond length of the proximal oxygen suggests that, as was observed in **147**, this movement could be primarily due to packing within the crystal structure rather than any physical interaction.

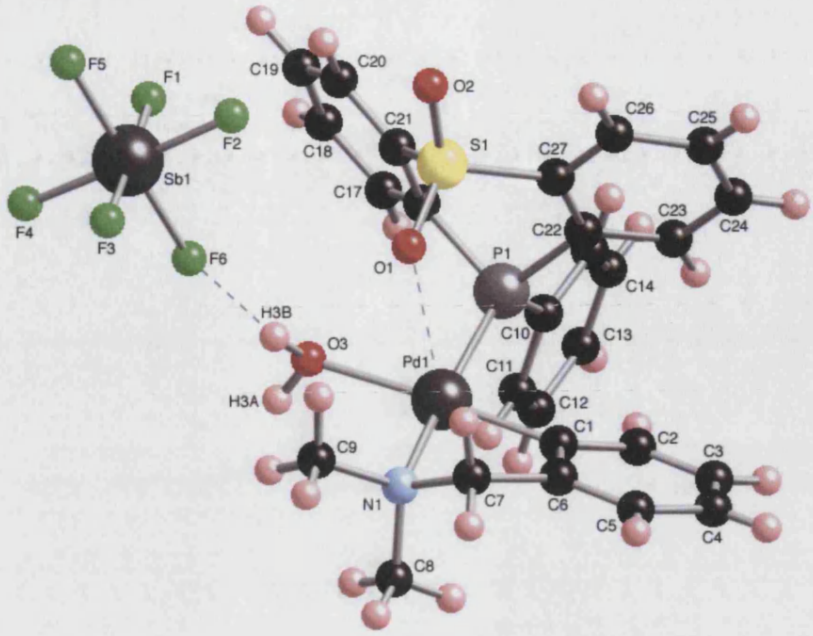


Figure 10 Molecular structure of complex **151**

Closer inspection of the 3-dimensional structures obtained for the three complexes indicated that the sulphone oxygen could not bind to the palladium centre due to steric hinderance, caused by the rigid nature of ligand **143**. Modeling shows that rotation about the P-Pd bond to position the sulphone oxygen close to that of the chloride in **147** would place the phenyl tail of **143** in very close proximity, possibly over, the phenyl ring of the dimethylbenzylamine (Figure 11).

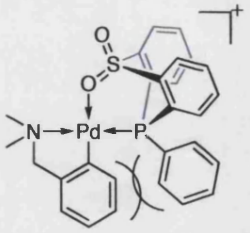
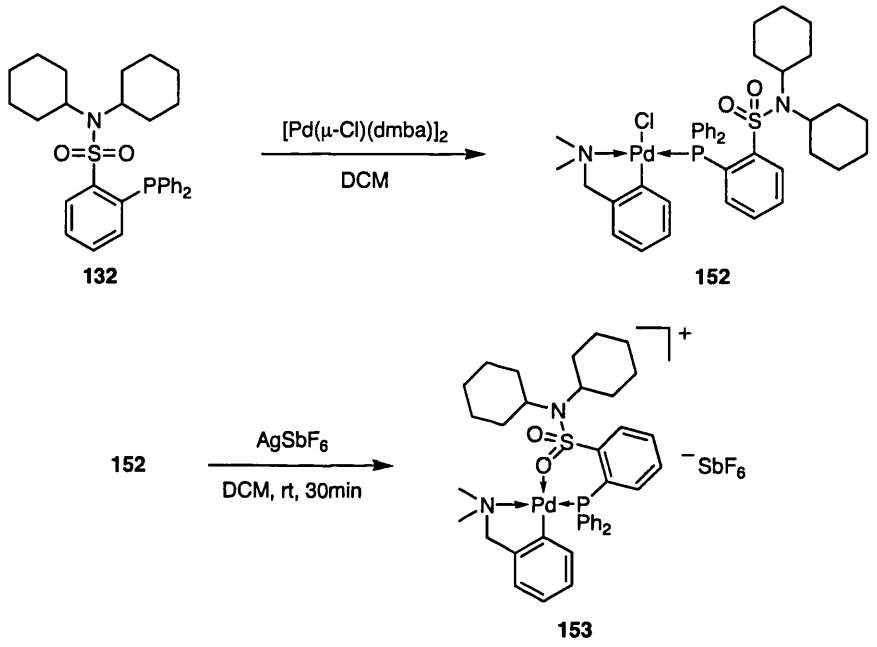


Figure 11 Possible interaction between the two phenyl rings, hindering direct coordination of the sulphone to palladium centre

The analogous reaction of ligand **132** with $[Pd(\mu\text{-}Cl)(dmba)]_2$ afforded the neutral chloride complex **152** (Scheme 87), as a pale green solid in 92% yield, with a $^{31}P\{^1H\}$ NMR signal at δ 46.07. Treatment of **152** with silver hexafluroantimonate ($AgSbF_6$) in anhydrous DCM for 30 minutes produced the cationic palladium complex **153** in 91%

yield (selected ^{1}H and $^{31}P\{^{1}H\}$ NMR data are presented in Table 3). Single crystal X-ray diffraction studies were performed on both complexes **152** (Figure 12) and **153** (Figure 13) with selected intramolecular distances and angles reported in Table A - 6 (Appendix 2). Conversely to that observed with ligand **143**, exchange of the chloride salt of **152** with a hexafluoroantimonate anion, results in the coordination of the sulphone to the palladium centre as shown in complex **153** (Scheme 87, Figure 13). Interestingly the $^{31}P\{^{1}H\}$ NMR signal also shifts upfield, from δ 46.07 to δ 33.40, the reverse to that predicted for a more Lewis acidic metal centre.



132 **152** **153**

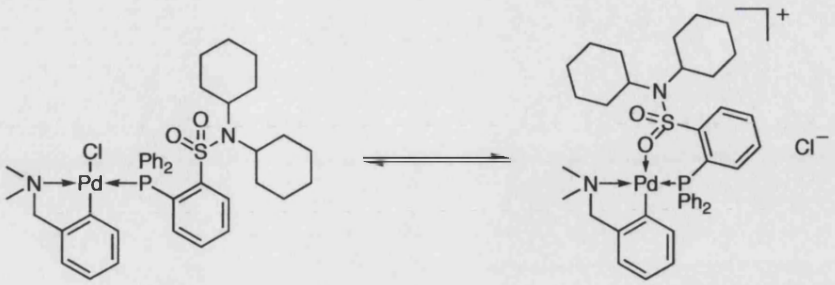
Scheme 87 Preparation of palladium complexes **152** and **153** with ligand **132**

Table 3 Seleced NMR data for ligand **132** and complexes **152** and **153**

Complex	Ligand	Salt	^{1}H NMR	$^{31}P\{^{1}H\}$ NMR
	132			-5.30
152	**132**	Cl^-	2.85 (6H, br s, CH_3) 3.80-4.40 (2H, v.br s, CH_2N)	46.07
153	**132**	SbF_6^-	2.85 (6H, d, $^{4}J_{PH}$ = 2.7, $N(CH_3)_2$) 4.09 (2H, s, NCH_2)	33.40

Interestingly, the ^{1}H NMR spectroscopic data for **152** displays broad signals for protons on carbons adjacent to the nitrogen of *N,N*-dimethylbenzylamine. These together with a slightly broad phosphorus signal suggest dynamic behaviour within the complex in the

solution phase; with the possible formation of the cationic Pd^{II} salt **152'** (Scheme 88). The single crystal X-ray diffraction data for **152** exhibits a single structure with the chloride ion bound to the palladium centre (Figure 12).



152 **152'**

Scheme 88 Possible dynamic behaviour in solution of complex **152**

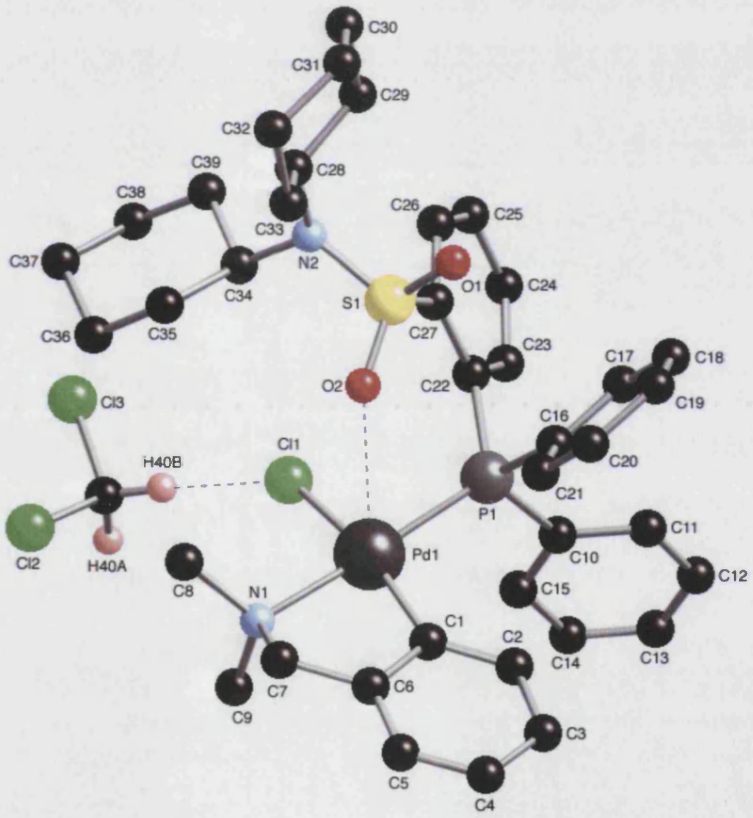


Figure 12 Molecular structure of complex **152** (hydrogens have been omitted for clarity)

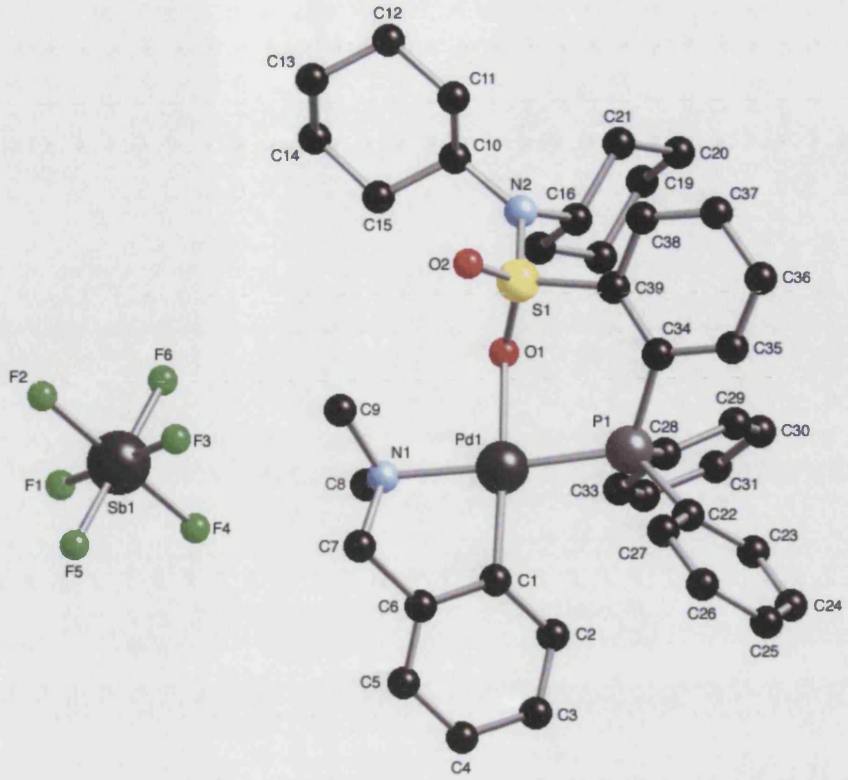


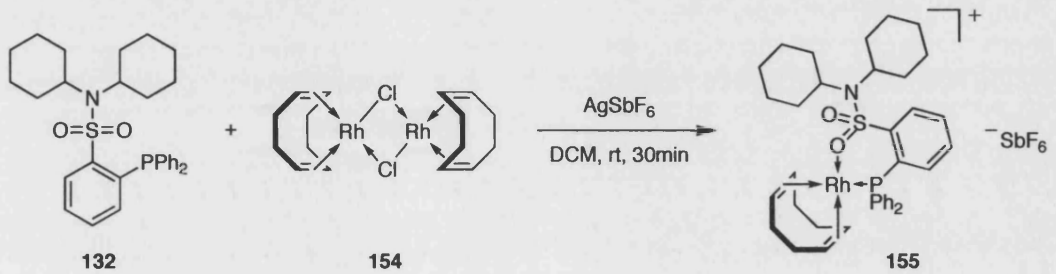
Figure 13 Molecular structure of complex **153** (hydrogens have been omitted for clarity)

Comparison of the crystallographic data for **152** and **153** (Table A - 6, Appendix 2) highlights the variations in interatomic distances expected for coordination through the sulphone. In complex **152** the Pd-O bond length (Pd(1)-O(2) 2.9454(14)Å) is too long for a definite interaction and is more akin to a weak coordination. Whereas the analogous distance in **153** (Pd(1)-O(1) 2.1508(13)Å) is shorter and can be assumed to be a significant interaction. Indeed the Pd-O bond length is shorter than for those observed between the palladium and triflate ion in **149** (2.2077(12)Å), and between the palladium and water molecule in **151** (2.2031(13)Å). As a result of the direct bonding between the sulphone and the palladium the S-O bond lengths have altered as predicted, with the coordinating oxygen to sulphur bond lengthening from 1.4379(13)Å to 1.4711(12)Å, and the unbound O-S bond unchanged at 1.4380(13)Å and 1.4307(12)Å.

Rhodium Complexes

Cationic rhodium complex **155** was prepared by the treatment of $[RhCl(COD)]_2$ **154** with ligand **132** and $Ag[SbF_6]$ in dichloromethane for 30 minutes (Scheme 89). Golden

red prisms were afforded which were suitable for X-ray diffraction analysis. As with the palladium SbF_6 salt, ligand **132** displayed coordination through the sulphone oxygen in the solid phase (Figure 14). Similarly, a longer S-O bond length was realised for the coordinated oxygen over that with the uncoordinated oxygen, 1.468(4)Å and 1.424(4)Å respectively. Selected intramolecular distances and angles are presented in Table A - 9 (Appendix 3). Interestingly, the Rh-O bond length in **155** is shorter and the Rh-P distance is longer than for the pailadium equivalent.



132 **154** **155**

Scheme 89 Preparation of cationic rhodium complex **155**

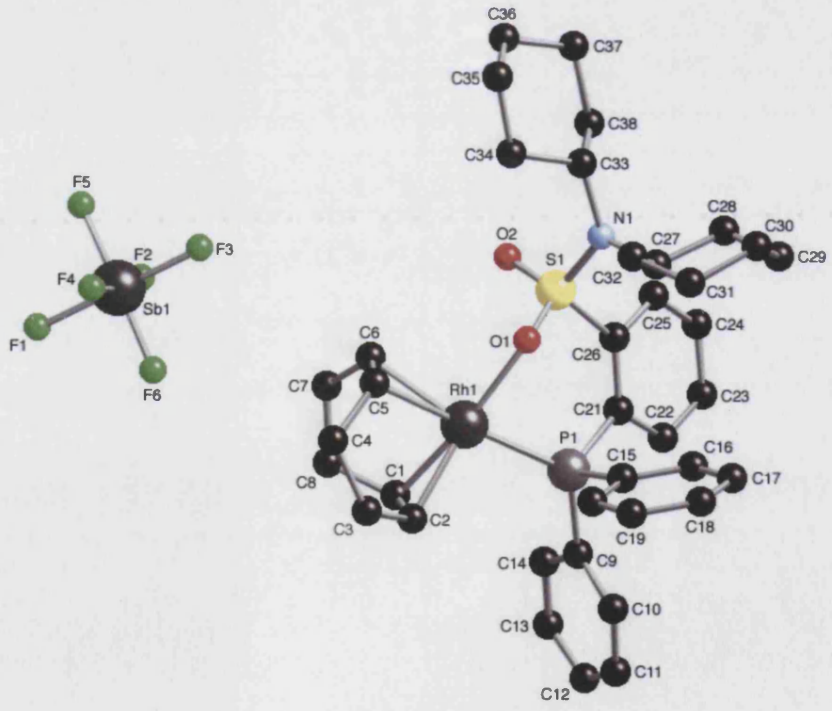


Figure 14 Molecular structure of rhodium complex **155** (hydrogens have been omitted for clarity)

2.6 CATALYTIC ACTIVITY ASSESSMENT IN THE SUZUKI-MIYAURA CROSS-COUPLING REACTION

2.6.1 Background

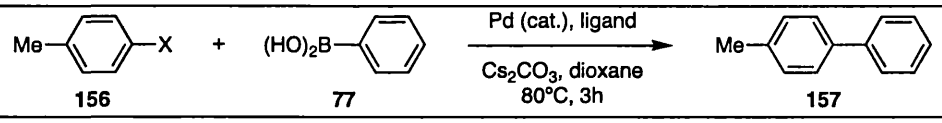
The Suzuki reaction has become a major synthetic tool for the organic chemist, as shown in Chapter 1.2.1, with numerous ligands and complexes having been tested for activity including palladacyclic complexes.[135] Guram and co-workers have reported the use of their hybrid P,O ligands as successful for both palladium catalysed amination and Suzuki reactions.[118,123,124] Thus with the new sulphone ligands in hand their activity in the Suzuki reaction was investigated.

2.6.2 Palladium-Catalysed Suzuki Couplings

An array of conditions have been applied to the Suzuki reaction since it was first introduced in 1979. During our studies the conditions presented by Nolan[106] were found to generate the products in highest yields. Thus, treatment of the arylhalide and boronic acid with a palladium source, ligand and caesium carbonate, in anhydrous dioxane for 3 hours at 80°C afforded the desired cross coupled products in high yields.

Initial experiments examined the coupling of 4-bromo- and 4-chlorotoluene with phenyl boronic acid. It was clear from the outset that all the ligands were poor activators for the oxidative addition of chlorotoluene, including the more basic dicyclohexyl phosphines **135** and **142** (Table 4). The palladium source used in the reaction had a substantial effect on the efficiency of the final palladium-ligand complex. The sulphonamide class of ligands exhibited greatest reactivity and generated higher isolated yields by the use of $[Pd_2(dba)_3]$ as the palladium source rather than $[Pd(OAc)_2]$. However, whilst ligand **143** displayed disappointingly low reactivity with $[Pd_2(dba)_3]$ (3%), the use of $[Pd(OAc)_2]$ or the preformed triflate salt **149**, gave a significant increase with 65-70% yield of the desired product isolated (Entries 1,2 and 5). Interestingly, ligand **146** displays greater activity than the more constrained **143** (Entries 2 and 18). 4-Methoxyphenylboronic acid is also effectively coupled under these reactions conditions with ligand **132** providing 4-methyl-4'-methoxybiphenyl in excellent yield (>99%) (Table 4, Entry 8).

Table 4 Selected results for the palladium catalysed Suzuki reactions with phenylboronic acid **77**[a]



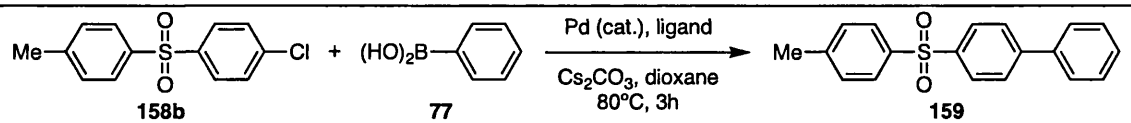
156 **77** **157**

Entry	Ligand	Palladium source	X	Yield (%)[b]
1	**143**	$[Pd_2(dba)_3]$	Br	3
2	**143**	$[Pd(OAc)_2]$	Br	69
3	**143**	$[Pd_2(dba)_3]$	Cl	<2
4	**143**	$[Pd(OAc)_2]$	Cl	8
5	-	**149**	Br	65
6	-	**149**	Cl	0
7	**132**	$[Pd_2(dba)_3]$	Br	99
8	**132**	$[Pd_2(dba)_3]$	Br	>99[c]
9	**132**	$[Pd(OAc)_2]$	Br	75
10	**132**	$[Pd_2(dba)_3]$	Cl	0
11	**132**	$[Pd(OAc)_2]$	Cl	3
12	**135**	$[Pd_2(dba)_3]$	Br	>99
13	**135**	$[Pd(OAc)_2]$	Br	94
14	**135**	$[Pd(OAc)_2]$	Cl	6
15	**142**	$[Pd_2(dba)_3]$	Br	99
16	**142**	$[Pd(OAc)_2]$	Br	95
17	**142**	$[Pd(OAc)_2]$	Cl	5
18	**146**	$[Pd(OAc)_2]$	Br	93
19	**146**	$[Pd(OAc)_2]$	Cl	5

[a] Typical reaction conditions: 1.0 equiv. of aryl halide, 1.5 equiv. of phenylboronic acid, 2.0 equiv. of Cs_2CO_3, 2 mol% Pd, 2 mol% ligand, dioxane (3mL/mmol halide), 80°C, 3 hours; [b] Isolated Yield; [c] 4-methoxyphenylboronic acid used in place of phenyl boronic acid **77**

Whilst disappointing results were obtained for the coupling of chlorotoluene with phenyl boronic acid, couplings with 1-chloro-4-tosylbenzene **158b** proceeded in higher yields (Table 5). As expected the more basic dicyclohexylphosphines, **135** and **142** afforded higher yields of the desired 1-phenyl-4-tosylbenzene **159**. Contrary to the activity of palladium sources observed in the coupling of bromotoluene, use of $[Pd(OAc)_2]$ gave superior yields over $[Pd_2(dba)_3]$.

Table 5 Palladium catalysed Suzuki reaction of arylchloride **158b** with phenylboronic acid **77**[a]



158b **77** **159**

Entry	Ligand	Palladium source	Yield (%)[b]
1	**135**	$[Pd_2(dba)_3]$	32
2	**135**	$[Pd(OAc)_2]$	72
3	**142**	$[Pd(OAc)_2]$	77
4	**146**	$[Pd(OAc)_2]$	3

[a] Typical reaction conditions: 1.0 equiv. of arylchloride, 1.5 equiv. of phenylboronic acid, 2.0 equiv. of Cs_2CO_3, 2 mol% Pd, 2 mol% ligand, dioxane (3mL/mmol halide), 80°C, 3 hours; [b] Isolated Yield

2.7 SUMMARY

In summary, a selection of novel modular, hybrid ligands have been synthesised containing the sulphone moiety. The sulphonamide ligands have been shown to be bidentate in the solid state, in palladium and rhodium complexes, with coordination displayed through both the phosphine and sulphonanmide oxygen. The ligands display reasonable activity when applied to the Suzuki-Miyaura reaction, with isolated yields equalling, and in selected cases, bettering those published in the literature for the identical reaction.[106] Whilst yields for the coupling with 4-chlorotoluene are low, the activated 1-chloro-4-tosylbenzene proved to be an effective partner for this reaction with isolated yields of up to 77% achieved. These results clearly show the phosphine-sulphone and phosphine-sulphonamide hybrid ligands to be effective ligands for the palladium catalysed Suzuki-Miyaura reaction.

CHAPTER THREE:

Synthesis of Unnatural α-Amino Acids Via the Rhodium Catalysed 1,4-Addition of Boronic Acids

3 Synthesis of Unnatural α-Amino Acids *via* the Rhodium-Catalysed 1,4-Addition of Boronic Acids

3.1 Aims and Objectives

The primary objective of this project was the synthesis of a range of α-amino acids from readily available starting materials, through the rhodium catalysed 1,4-conjugate addition of boronic acids to activated alkenes. Ultimately these reactions will be enantioselective and accommodate a range of functional groups on both the boronic acids and the amino acid backbone.

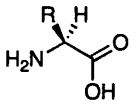
3.2 Envisaged Programme of Work

Initial studies will focus on the racemic synthesis of α-amino acids derivatives, through the study of a range of rhodium complexes and conditions. Analogy of this reaction with that of the rhodium catalysed 1,4-conjugate addition to enones and related structures, *vide supra* (Chapter 1.3.1), will form the basis of further studies in the asymmetric addition to form amino acids. After optimisation of the conditions has been established a range of amino acids will be prepared from a library of boronic acids.

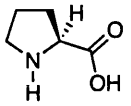
3.3 Background

The α-amino acids, are undoubtedly the most significant, numerous and diverse family of the naturally occurring amino acids. A set of twenty comprise the building blocks from which proteins, peptides and biopolymers (responsible for both structure and function of most living things) are constructed under genetic control. Nineteen of the twenty are primary amines differing only in the nature of the side chain substituents, with the final one, proline, a secondary cyclic amine. However, the total number of α-amino acids identified as occurring free or incorporated in the natural products of plants, animals and micro-organisms is diverse and estimated to be in the hundreds,

with the catalogue of such α-amino acids increasing all the time. Typically naturally occurring α-amino acids exhibit the L-configuration at the α-carbon. α-Amino acids whose configuration is that of D are characteristically encountered in non-protein compounds of plants and micro-organisms with a few examples in animals, although never in animal proteins.



General structure of a primary α-amino acid

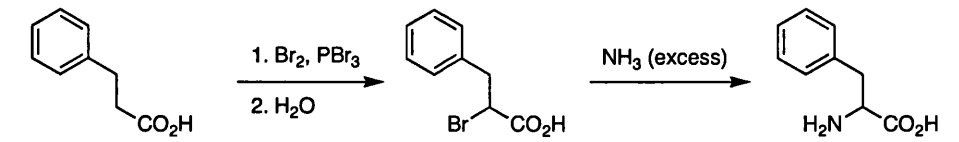


Proline, a secondary α-amino acid

Amino acids are elemental building blocks for the preparation of many natural products and their analogues, as such the synthesis of both natural and novel variants has for a long time perplexed many a synthetic chemist. A variety of methods have been developed for the synthesis of amino acids, utilising both more *traditional* chemical synthesis and recently the application of transition metal catalysis. Classical methods for the synthesis of α-amino acids include:[136]

Displacement reactions on α-halo acids.

α-bromination of carboxylic acids with bromine and phosphorus tribromide (the Hell-Volhard-Zelinskii reaction) affords α-bromoacids which upon treatment with an excess of ammonia undergo nucleophilic substitution to yield the α-amino acid (Scheme 90). Alternatively, phthalimide can be used in the place of ammonia *via* the Gabriel amine synthesis method.



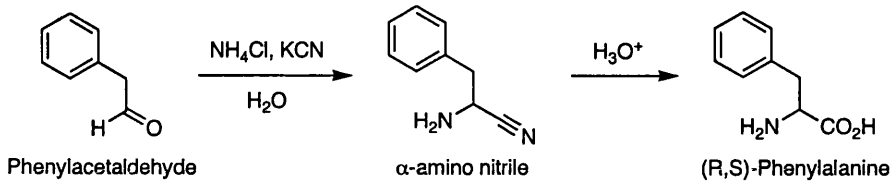
3-phenylpropanoic acid — 2-bromo-3-phenyl-propanoic acid — (R,S)-Phenylalanine

Scheme 90

The Strecker synthesis.

Developed in 1850, the Strecker synthesis is possibly one of the most well known synthetic routes to α-amino acids. The route involves a two-step process; treatment of an aldehyde with potassium cyanide and aqueous ammonia to afford

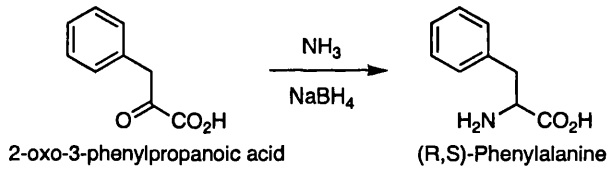
an intermediate α-amino nitrile, whose hydrolysis generates the α-amino-acid (Scheme 91).



Scheme 91

Reductive amination

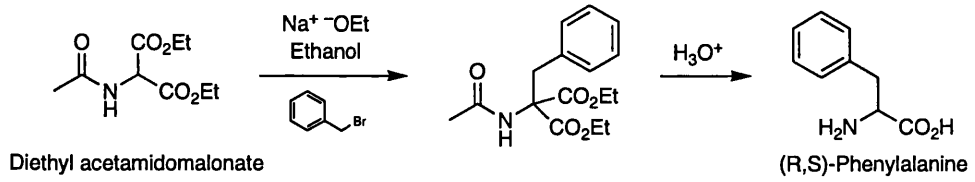
The reductive amination method of α-amino acids is particularly interesting since it is a close synthetic analogy of a pathway by which some amino acids are biosynthesised in nature. Treatment of an α-keto acid with ammonia and a reducing agent such as sodium borohydride, generates the desired racemic amino acid (Scheme 92).



Scheme 92

Amidomalonate synthesis

Possibly the most general traditional method for the synthesis of α-amino acids is the amidomalonate synthesis. An extension of the malonic ester synthesis, the methodology involves the conversion of diethyl acetamidomalonate to its enolate anion, through the treatment with base. A subsequent S_N2 reaction with a primary alkyl halide, affords the alkylated malonic ester, which upon hydrolysis and decarbonylation when heated in aqueous acid, forms the racemic amino acid (Scheme 93).

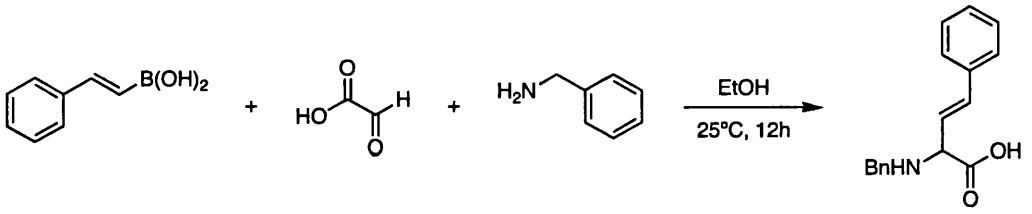


Scheme 93

Among the more recently published methods for the synthesis of α-amino acids are the:

Petasis boronic acid method

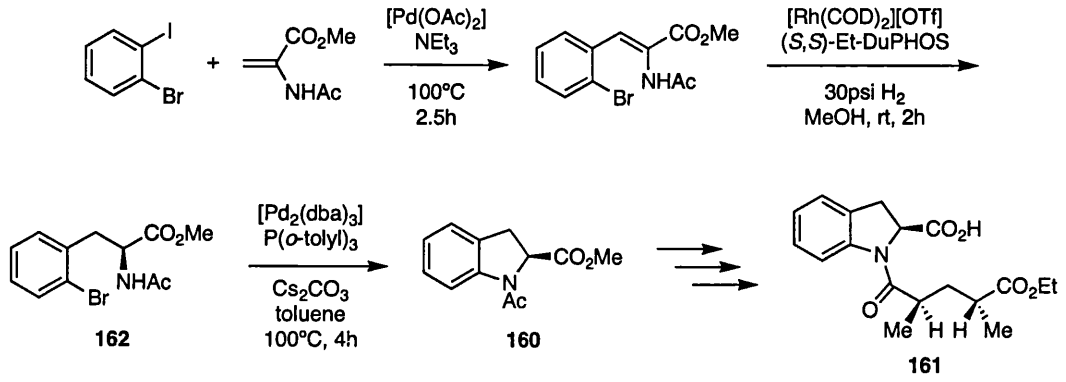
The multi-component reaction of boronic acids with imine or iminium species (generated *in situ* by the reaction of amines with glyoxylic acid), known as the Petasis reaction, is a simple and efficient route to the synthesis of phenyl- and vinyl-glycine derivatives.[137] For example the reaction of trans-2-phenylvinylboronic acid with glyoxylic acid and benzylamine affords *N*-benzyl-(*E*)-2-phenylvinylglycine (Scheme 94).



Scheme 94

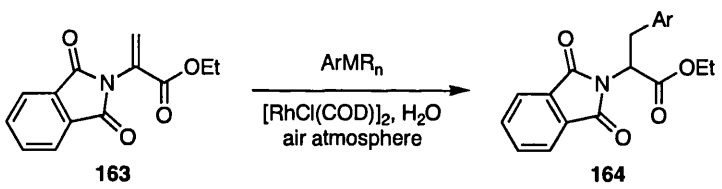
Catalytic hydrogenation of amino acrylates

The modification of Wilkinson's catalyst for olefin hydrogenation, with optically active phosphine ligands represents a field of study at the leading edge of asymmetric synthesis. Asymmetric hydrogenation of α-dehydroamino acids with rhodium complexes to form the corresponding α-amino acid has become an area of great interest for a range of organometallic chemists. Buchwald has reported its use in the synthesis of (*S*)-*N*-acetylindoline-2-carboxylate methyl ester **160**, a key intermediate in the synthesis of the ACE inhibitor **161** (Scheme 95).[138] With optically active phenylalanine derivative **162** prepared in two steps by a Heck addition followed by a rhodium-catalysed asymmetric hydrogenation of the resulting enamide.



Scheme 95

Recently Li has reported the synthesis of a range of α-amino acids *via* the rhodium catalysed conjugate addition of carbon nucleophiles to α,β-dehydroamino acid derivatives (Scheme 96).[139,140] Treatment of the electron deficient, ethyl α-phthalimidoacrylate **163** with $[RhCl(COD)]_2$ and organotin, organosilicon or organobismuth reagents in aqueous conditions generated the α-amino acid derivatives **164** in high yields. Tri-aryl bismuth reagents were found to afford higher yields when heated to reflux, whereas phenyltin derivatives recorded higher yields when sonicated at ambient temperature.

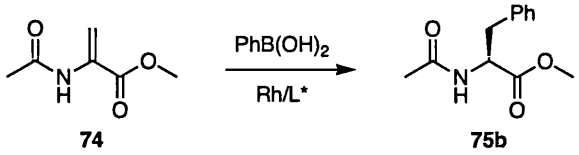


$ArMR_n$	Conditions	Yield (%)
Ph_3Bi	H_2O, reflux, overnight	72
Ph_3Bi	H_2O, rt, sonication, 2h	45
$PhSnMe_3$	H_2O, reflux, overnight	18
$PhSnMe_3$	H_2O, rt, overnight	0
$PhSnMe_3$	H_2O, rt, sonication, 2h	82
$PhSnMe_3$	dioxane, rt, sonication, 2h	11

Scheme 96

Whilst this methodology presents the mild preparation of phenylalanine derivatives, the use of toxic tin and wasteful triarylbismuths reagents, with just one aryl group transferred during the reaction, significantly reduces the general applicability of this reaction. These drawbacks could be overcome by the application of boronic acids.

Reetz has performed a single example of this type of addition preparing the protected phenylalanine **75b** from methyl-2-acetomidoacylate **74** *vide supra* (Chapter 1.3.1) (Scheme 97). Surprisingly the addition of boronic acids to ethyl α-phthalimidoacrylate and derivatives thereof has not been previously investigated.

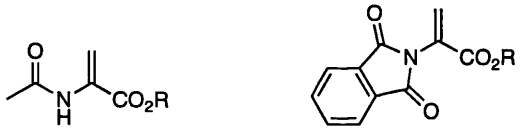


74 **75b**

Scheme 97

3.4 RACEMIC RHODIUM CATALYSED 1,4-ADDITIONS

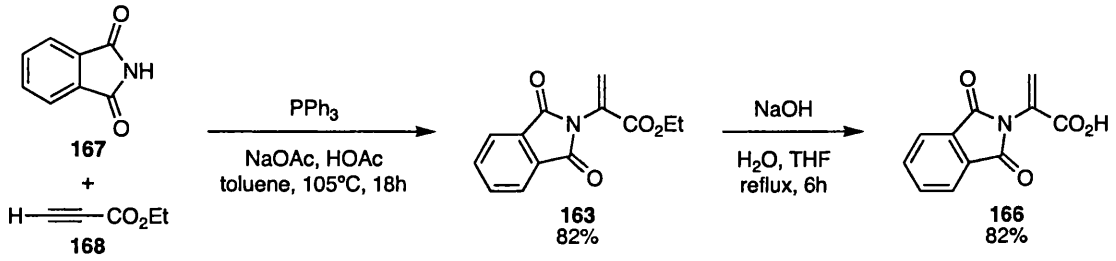
Initial experiments examined the rhodium-catalysed addition of 1-naphthaleneboronic acid to dehydroalanine derivatives **74**, **163**, **165** and **166**, using the conditions presented by Li, those of refluxing the aqueous suspension for 18-24 hours under an air atmosphere. Whilst **165** and **74** are commercially available, **166** and **163** have to be synthesised.



R = Me **74** R = Et **163**

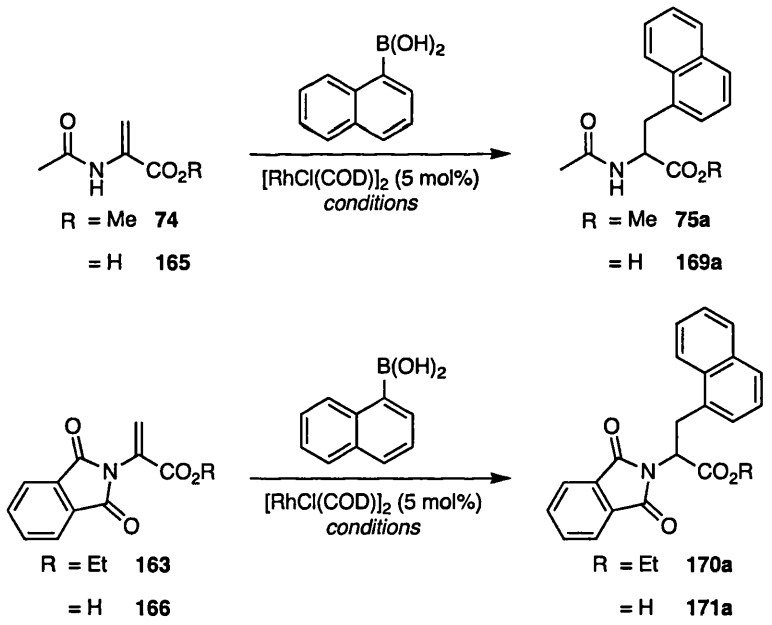
= H **165** = H **166**

Ethyl-α-phthalimidoacrylate **163** was prepared as described by Trost and Dake.[141] Heating a 1:1 mixture of ethyl propiolate and phthalimide at 105°C in toluene with 10 mol% triphenylphosphine and a 1:1 sodium acetate-acetic acid buffer, gave the desired dehydroalanine in 82% yield. Subsequent saponification of the ethyl ester in aqueous sodium hydroxide afforded the free acid also in 82% yield (Scheme 98).



Scheme 98 Synthesis of enamides **163** and **166** from phthalimide **167** and ethyl propiolate **168**

With the dehydroalanine derivatives in hand, the investigations concerning the viability of the use of boronic acids as aryl nucleophiles were commenced (Scheme 99, Table 6). It was apparent form the outset that the presence of a free carboxylic acid group had an unfavourable effect on the reaction's capability (Entries 1 and 3). Rationalisation for this observation is based on the probable oxidative addition of the carboxylic acid followed by proteolytic cleavage of the rhodium-aryl bond, forming naphthalene, which is a significant product observed from the reactions.



Scheme 99 Rhodium-catalysed conjugate addition to dehydroalanine derivatives

In accordance with the observations of Li and Haung, the utilisation of ethyl-α-phthalimidoacrylate **163** provided the addition product in excellent yield (Entry 4). The increased efficiency when coupling with **163** compared to **74** is due to the enhanced stability of the phthalyl group in the presence of the mildly acidic aqueous conditions of the reaction. Recent advances by Lautens in the coupling of boronic acids with

heteroaromatic olefins in aqueous media has highlighted the use of the phase transfer catalyst sodium dodecylsulphate (SDS) as an important component, enhancing the reaction yield *vide supra* (Chapter 1.3.2).[89] Similarly, the reaction proceeded in the presence of catalytic quantities of SDS, however yields were reduced slightly compared to the reaction without SDS, 89% and 98% respectively (Table 6, Entries 5 and 4). Remarkably the reaction can be performed with catalyst loadings lowered to 0.5 mol% $[RhCl(COD)]_2$ with no significant loss in efficiency.

Table 6 Rhodium-catalysed synthesis of amino acid derivatives

Entry	Enamide	Conditions	Product	Yield (%)[b]
1	**165**	H_2O, 100°C, 24 hours	**169a**	<5
2	**74**	H_2O, 100°C, 24 hours	**75a**	30
3	**166**	H_2O, 100°C, 24 hours	**171a**	<5
4	**163**	H_2O, 100°C, 24 hours	**170a**	98
5	**163**	H_2O, SDS, 100°C, 24 hours	**170a**	89
6[c]	**163**	H_2O, 100°C, 24 hours	**170a**	92

[a] Typical reaction conditions: enamide (0.25 mmol), naphthaleneboronic acid (0.5 mmol), $[RhCl(COD)]_2$ (5 mol%), H_2O (3 mL), 100°C, 24 hours; [b] Isolated yield after flash chromatography; [c] 0.5 mol% $[RhCl(COD)]_2$

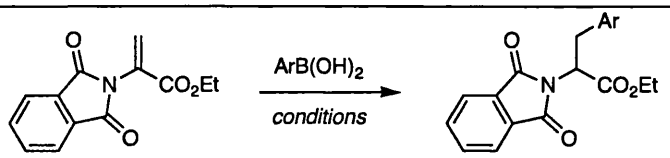
Further investigations into the addition of 1-naphthaleneboronic acid to enamide **163** highlighted the need for the rhodium catalyst to be coordinated by substitutionally inert groups (Table 7). Exchange of 1,5-cyclooctadiene with the more labile cyclooctene the catalyst barely turned over with just 6% isolated yield recorded (Table 7, Entry 2). The application of preformed cationic rhodium-phosphine salts afforded high yields (Entries 3-5). Interestingly, sulphonamide ligand **132** efficiently catalyses the reaction with activity equivalent to that of BINAP. Variation of the counterion of the rhodium complex had no effect on the observed activity with both SbF_6 and OTf affording ~90% isolated yields. The reaction was also found to be efficient when performed in anhydrous 1,4-dioxane. Whilst the addition of K_3PO_4 was not essential for the reaction, multiple unwanted side products were observed in its absence. Although no water is directly added to the reaction mixture, it is thought that upon heating the boronic acid forms the cyclic boroxine anhydride with the condensation of water in the process. This water is proposed to enable the catalytic turn over of the reaction.

Due to the high yields associated with the use of 1-naphthaleneboronic acid the effect of solvent variation is not fully realised. The use of phenylboronic acid, however enabled a fuller picture to be appreciated (Entries 9-12). Whilst the yield obtained by perfoming the coupling of phenylboronic acid in water, is reduced slightly over that achieved with

1-naphthaleneboronic acid, 86% and 98% respectively (Entry 9), the application of the anhydrous 1,4-dioxane conditions retains the high yields (Entry 10). Use of mixed solvent systems however, sees a dramatic reduction in activity of the process with 60 and 41% yields obtained for aqueous 1,4-dioxane and 1,2-dimethoxylethane (DME) solutions respectively (Entries 11 and 12).

Although marginally higher yields could be obtained with the use of anhydrous 1,4-dioxane and base over simply water, the benefit was deemed on a par with that of performing the reaction under an air atmosphere in non-toxic water. Thus for operational simplicity further reactions would be preferentially performed in water at reflux.

Table 7 Effect of conditions and rhodium complex on the synthesis of amino acids from enamine **163**[a]



163 **170**

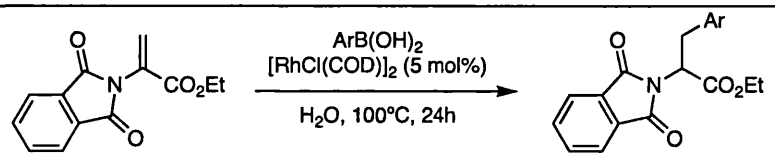
Entry	Conditions	Rhodium source	Ar	Yield (%)[b]
1	H_2O, 100°C, 24h	$[RhCl(COD)]_2$	1-naphthalene	98
2	H_2O, 100°C, 24h	$[RhCl(COE)_2]_2$	1-naphthalene	6
3	H_2O, 100°C, 24h	[Rh**132**(COD)][SbF_6] (**155**)	1-naphthalene	88
4	H_2O, 100°C, 24h	[Rh**132**(COD)][OTf]	1-naphthalene	89
5	H_2O, 100°C, 24h	[Rh(BINAP)(COD)][SbF_6]	1-naphthalene	90
6	H_2O, rt, 24h	$[Rh(OH)(COD)]_2$	1-naphthalene	18
7	dioxane, K_3PO_4, N_2, 100°C, 24h	$[RhCl(COD)]_2$	1-naphthalene	99
8	dioxane, N_2, 100°C, 24h	$[RhCl(COD)]_2$	1-naphthalene	93
9	H_2O, 100°C, 24h	$[RhCl(COD)]_2$	phenyl	86
10	dioxane, K_3PO_4, N_2, 100°C, 24h	$[RhCl(COD)]_2$	phenyl	95
11	dioxane-H_2O (1:1), 100°C, 24h	$[RhCl(COD)]_2$	phenyl	60
12	DME-H_2O (1:1), 100°C, 24h	$[RhCl(COD)]_2$	phenyl	41

[a] Typical reagent quantities: enamide (0.25 mmol), $ArB(OH)_2$ (0.5 mmol), [Rh] (5 mol%), solvent (3 mL); [b] Isolated yield after flash chromatography;

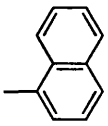
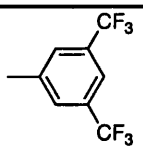
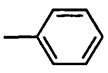
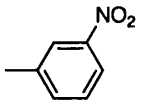
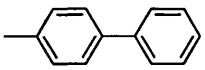
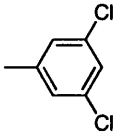
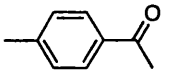
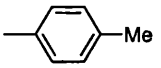
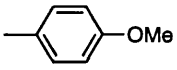
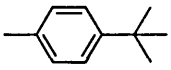
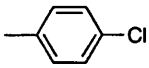
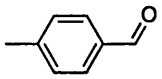
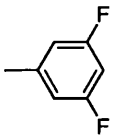
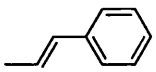
Under the preferred reaction conditions the scope of the methodology was explored with respect to the boronic acid used (Table 8). The reaction proceeded well in all cases generating a variety of unnatural α-amino acid derivatives in good yield. It should be noted that both electron-withdrawing and donating groups can be accommodated on the boronic acid. Both boronic acids and potassium trifluoroborate salts were efficiently coupled under the conditions employed (Entry 2). Of particular interest was the coupling of 4-formylphenylboronic acid (Entry 13), especially given that rhodium complexes are known to promote the addition of boronic acids to aldehydes, *vide supra*

(Chapter 1.3.3). Seemingly under the aqueous conditions used the 1,4-conjugate addition occurs preferentially over that of the 1,2-addition, without the protection of the aldehyde required. Incorporation of functionalities such as aldehydes, nitro groups and halides provide both pharmacologically interesting products and the opportunity for further elaboration. The ability to efficiently couple alkenylboronic acids is also of interest (Entry 14), with hydrogenation of the resulting products forming a route to the synthesis of alkane substituted amino acids in addition to providing an additional handle for further derivatisation.

Table 8 Synthesis of amino acid derivatives from **163**[a]



163 **170a-n**

Entry	Ar		Yield (%)[b]	Entry	Ar		Yield (%)[b]
1		**170a**	98	8		**170h**	90
2		**170b**	86 78[c]	9		**170i**	66
3		**170c**	89	10		**170j**	93
4		**170d**	70	11		**170k**	77
5		**170e**	88	12		**170l**	73
6		**170f**	66	13		**170m**	59
7		**170g**	85	14		**170n**	96

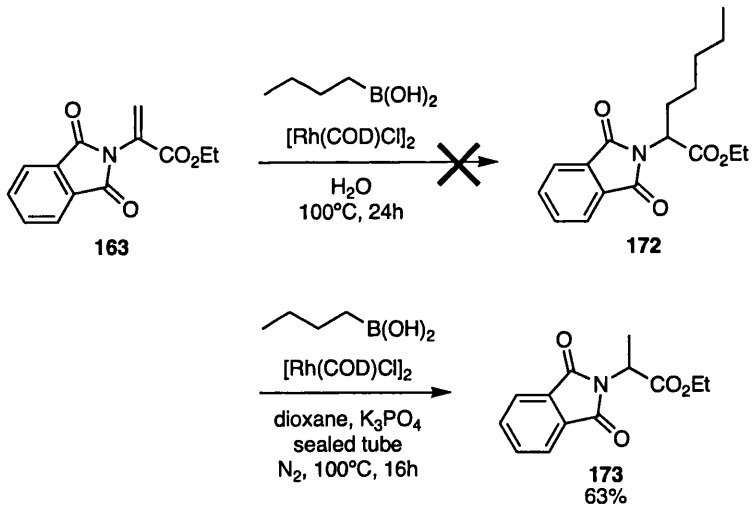
[a] Typical reaction conditions: enamide **CA** (0.25 mmol), $ArB(OH)_2$ (0.5 mmol), $[RhCl(COD)]_2$ (5 mol%), H_2O (3 mL), 100°C, 24 hours; [b] Isolated yield after flash chromatography; [c] $PhBF_3K$ salt used in place of $PhB(OH)_2$

The protecting groups can be cleaved either selectively by a two step process of ester hydrolysis followed by the hydrazine removal of the phthalyl group, or the simultaneous removal of both protecting groups under acidic conditions to furnish the hydrochloride salt in excellent yields.[142]

Addition of Alkylboronic Acids.

Whilst the addition and subsequent hydrogenation of alkenylboronic acid would provide a synthetic means to produce α-amino acids encompassing alkyl side chains, a far more elegant route would be the direct conjugate addition of alkylboronic acids to the dehydroamino acid. Whilst conjugate additions of alkyl groups to this type of structure have been performed before with organocuprates,[143] alkylboronic acids have yet to be coupled effectively.

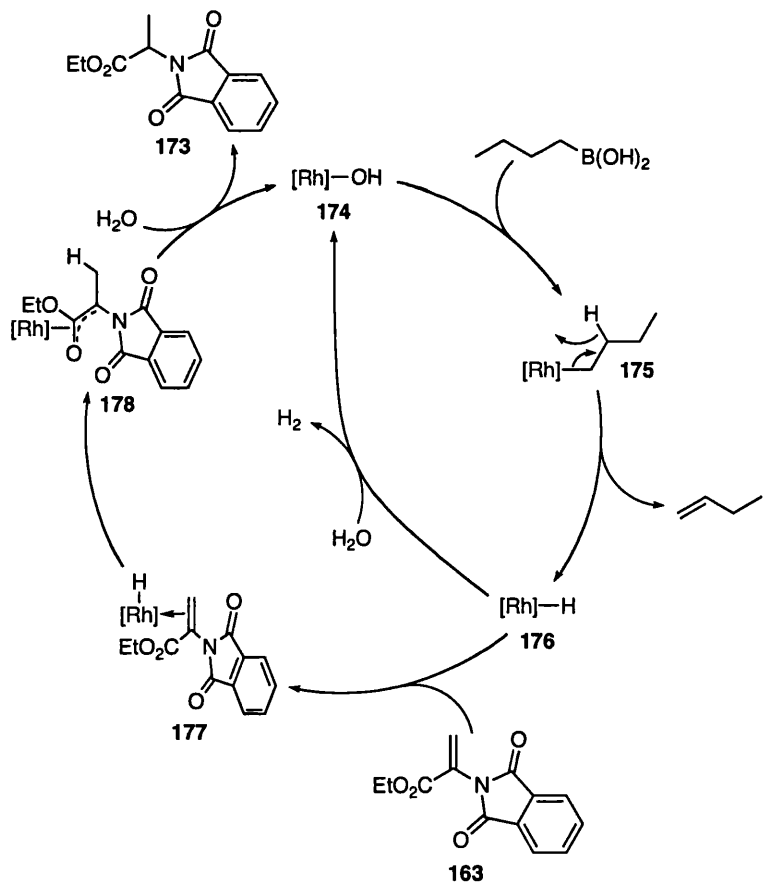
Investigations concerned with the addition of *n*-butylboronic acid to ethyl-α-phthalimidoacrylate under the preferred aqueous conditions afforded none of the desired coupled product **172**, with the starting acrylate fully recovered after purification by flash chromatography. However, when the reaction was performed in anhydrous 1,4-dioxane with K_3PO_4 under a nitrogen atmosphere in a pressure tube, the reduced product **173** was generated in 63% isolated yield (Scheme 100).



Scheme 100

The generation of **173** can be rationalised by β-hydride elimination from the rhodium alkane complex **175** (Scheme 101). The occurrence of β-hydride elimination is well documented both for rhodium[90,144] and other transition metals.[145] Formed by the

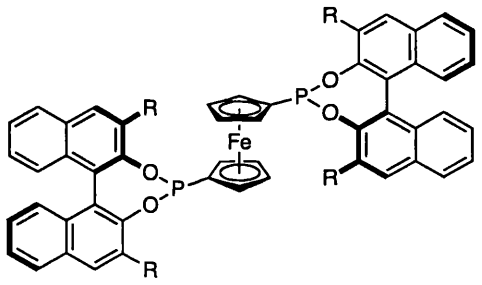
transmetallation of butylboronic acid with rhodium hydroxide **174**, **175** can undergo β-hydride elimination generating butene and the rhodium hydride species **176** (Scheme 101). Hydrolysis of hydridorhodium **176** would generate molecular hydrogen and the catalytically active hydroxide species **174**. Alternatively, **176** could react with enamide **163** to give **178**, subsequent hydrolysis by water generates the reduced product **173** and regenerate the active hydroxorhodium species **174**. Given that the reduced product was not observed when performed under ambient pressure, the hydrolysis of **176** is proposed to be the kinetically preferred route. However when the reaction is performed in a sealed environment once the pressure within the tube achieves a certain pressure the reaction with enamide **163** becomes kinetically favourable. It should be noted that a release of pressure was observed when the sealed tube was opened. The reduced product could also be formed by the more widely accepted transition metal-catalysed hydrogenation mechanism with the H_2 produced.[146]



Scheme 101 Proposed mechanism for the reduction of enamide **163** with alkyl boronic acids

3.5 ENANTIOSELECTIVE RHODIUM-CATALYSED 1,4-ADDITIONS

Chapter 1.3 introduced the rhodium catalysed conjugate addition of arylboronic acids to organic electrophiles. Whilst high enantioselectivities have been achieved, typically α-disubstituted activated alkenes have not been employed as substrates owing to the lower reactivity. However, Hayashi and co workers have reported the effective addition of arylboronic acids to nitrocyclohexene,[84] affording products with high enantio- and diastereoselectivities controlled by protonation. In addition to this, work by Reetz *et al.* highlights the asymmetric addition to methyl-2-acetamidoacrylate to prepare the naturally occurring amino acid phenylalanine.[70] Importantly, Reetz noted the application of BINAP-derived rhodium catalyst afforded excellent activity (100% conversion) but a racemic product, contrary to what Hayashi observed with additions to nitrocyclohexene. Reetz also observed that the less electron rich diphosphonite ligands such as **76b** afforded 37% ee increasing to 77% ee when diphosphonite ligand **76a** derived from 3,3'-dibromo-1,1'-binaphthyl-2,2'-diol was used.



R = Br **76a**
= H **76b**

With the majority of rhodium catalysed conjugate additions the enantioselectivity achieved is a direct result of the facial selectivity of the coordinating alkene, and subsequent orientation of the alkene on the rhodium complex when the aryl group is transferred to it. However, with α-substituted alkenes the enantioselectivity is influenced by both facial selectivity and the protonation step. Often described as just the hydrolysis of the rhodium enolate complex to generate the conjugate addition product, this important step has been the subject of very few investigations. Indeed it is unknown

as to whether the proton originated from reaction medium[147] or the rhodium centre[148] itself, after the oxidative addition of water has transpired.

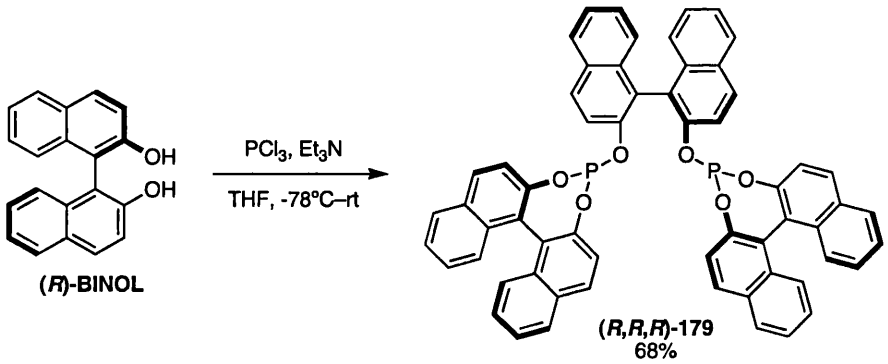
3.5.1 Synthesis of Ligands

Given the low selectivity reported by Reetz for BINAP, and the increased activity of diphosphonite ligands, it was postulated that ligand design would have a major effect on the enantioselectivity of the system and thus a series of BINOL based phosphite, phosphonite and phosphoramidite ligands were prepared to investigate this effect.

Phosphite Ligands

Studies concerning the phosphite ligands centred on the modular back-bone of the type displayed by diphosphite **179**. Ligand **179** was first reported by Pringle and Baker for nickel-catalysed hydrocyanation reactions[149] and has since been used in a number of enantioselective catalytic processes.[150,151]

Ligand **(*R*,*R*,*R*)-179** was prepared by established literature methods, by the dropwise addition of (*R*)-BINOL, in THF, to a cooled solution of phosphorus trichloride and triethylamine, in 68% yield (Scheme 102).[149] **(*S*,*S*,*S*)-179** was similarly prepared to asses whether any unexpected natural selectivity was inherent within the system.

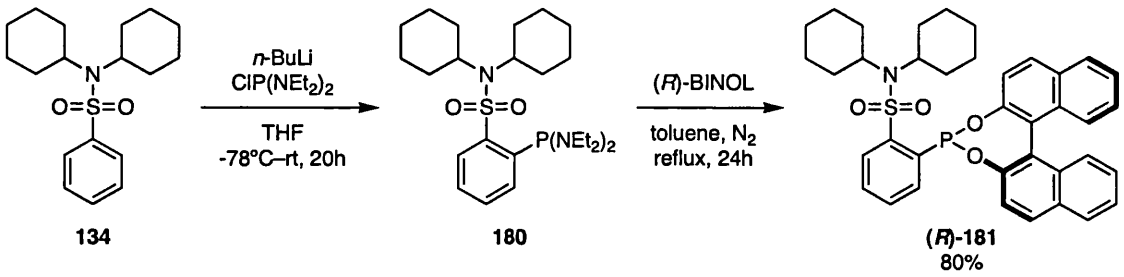


Scheme 102 Synthesis of diphosphite ligand **179**

Phosphonite Ligands

Encouraged by the high activity of the previously prepared sulphonamide ligand **132** in the racemic reaction (Table 7, Entries 3 and 4), the addition of a chiral moiety to the sulphonamide backbone was proposed to extend the applications for these novel

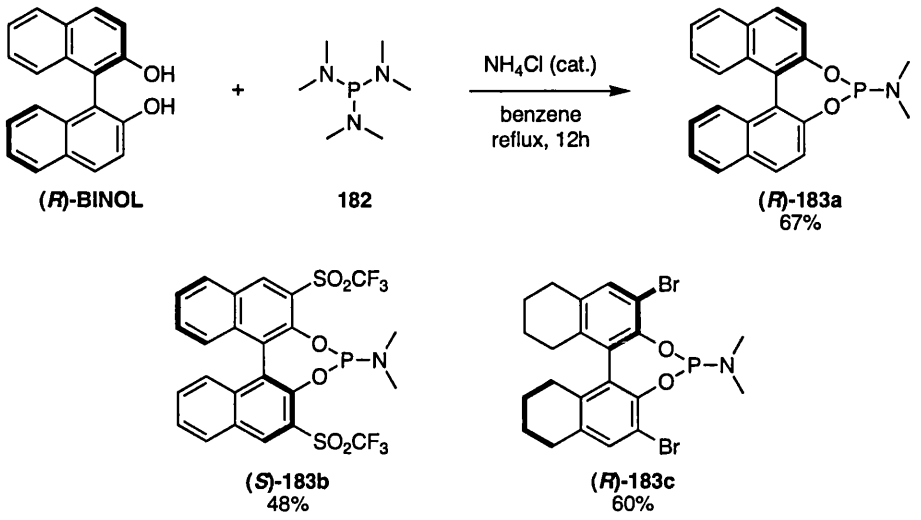
ligands. Due to the modular nature of the ligands this could either be integrated at the sulphonamide or phosphorus. However, due to the low activity reported by Reetz for phosphine ligands and the proposed hemilabile nature of the sulphonamide, it was deemed that inclusion of a chiral amine may be too distant from the coordinated metal centre and thus would be ineffective. Assimilation of chirality at the phophine was proposed by the addition of a BINOL group to a bisdiethylamidophosphine intermediate **180** (Scheme 103). Phosphination of **134** with chlorobisdiethylaminophosphine gave intermediate **180**, whose subsequent reaction with BINOL in refluxing toluene afforded the desired chiral ligand **(*R*)-181** in 80% yield, over the two steps.



Scheme 103

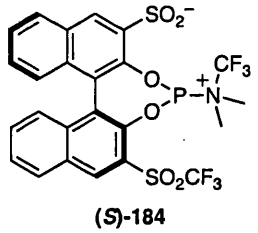
Phosphoramidite Ligands

Considered by many for some time as ineffective enantioselective catalysts, monodentate ligands have recently seen a change in fortune with enantioselectivities and rates comparable to or better than those obtained with bidentate ligands recently reported.[152] Originally utilised as ligands for the copper-catalysed enantioselective conjugate addition of organometallic reagents.[153] Phosphoramidite ligands have since been applied to the rhodium catalysed hydrogenation[152,154,155] and conjugate addition reactions.[65,67] Whilst the amine and diol moieties can take any form, our studies focused on the use of BINOL derivatives as the diol with dimethylamine as the amine of choice. Three BINOLs with varying bulk at both the 3,3'-position and in the terminal rings of the naphthyl rings were synthesised. Prepared by refluxing a benzene solution of the BINOL with hexamethylphosphorustriamide (HMPT) **182** and a catalytic quantity of ammonium chloride, ligands **183a-c** were generated in moderate yields (Scheme 104).[156]



Scheme 104 Synthesis of phosphoramidite ligands **183a-c**

Interestingly the NMR data for **183b** indicates an interaction between the phosphorus and one of the trifluoromethyl groups, with the $^{31}P\{^{1}H\}$ NMR containing a quartet with a coupling of 5.3Hz at δ 157.2, and the ^{19}F NMR showing two distinct fluorine environments, one a singlet at δ –76.9 and the other a doublet at δ –76.8 (J = 5.3 Hz). Furthermore, the signal for the amine methyl's in the ^{1}H NMR was very broad. These spectroscopic techniques seemed to indicate the possibility that one of the trifluoromethyl groups had been detached from its sulphone and subsequently coordinated to the amine, as presented in the structure of **184**.



(*S*)-184

However, single crystal X-ray analysis elucidated the structure to be that of the expected phosphoramidite **183b** (Figure 15). Rationale for the observed spectroscopic abnormalities in the NMR data is attributed to through space interactions in the solution phase.

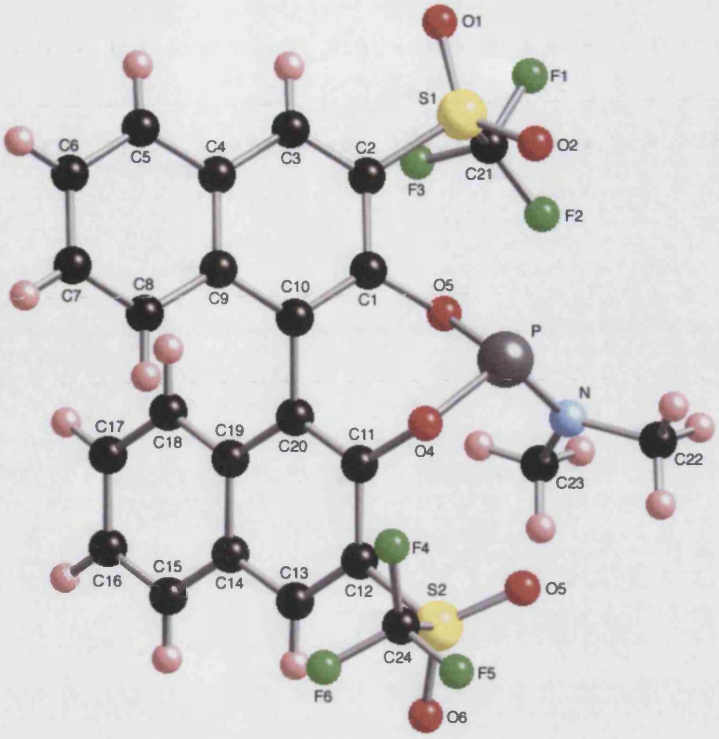
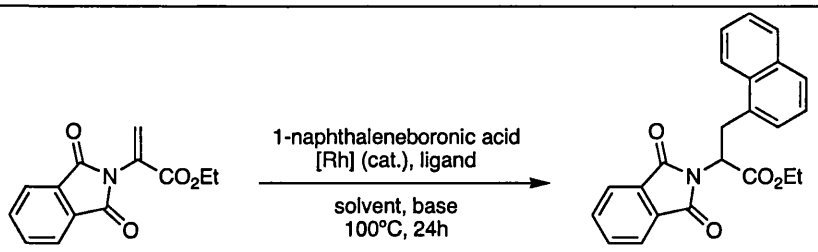


Figure 15 Molecular structure of phosphoramidite ligand **183b**

3.5.2 Enantioselective Catalytic Results

Initial studies focused on the addition of 1-naphthaleneboronic acid to ethyl-α-phthalimidoacrylate **163**; selected results are shown in Table 9. Whilst the majority of the reaction conditions assessed, provided the coupled product in high yields, disappointingly, the greatest enantioselectivity achieved was a mere 13% (Entry 4). Interestingly catalysts formed *in situ* typically gave marginally greater enantioselectivities over those with preformed cationic rhodium complexes. It is postulated that this trend is a direct result of the counter ion present, with more Lewis acidic rhodium associated with the more weakly coordinating SbF_6 anion displaying a lower selectivity than the less Lewis acidic centres of the chloride and hydroxide salts (Entries 2-4).

Table 9 Asymmetric synthesis of amino acid derivatives from **163**[a]

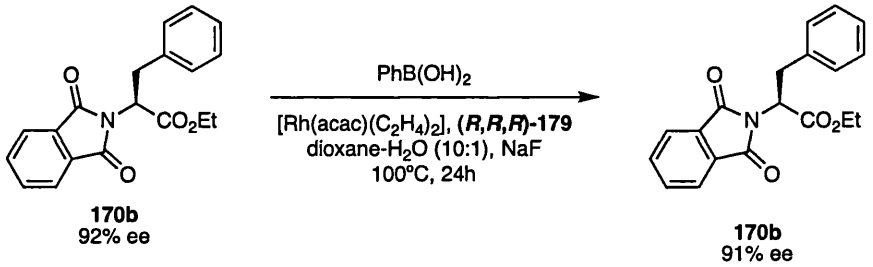


163 **170a**

Entry	Rhodium source	Ligand	Conditions	Yield (%)[b]	ee (%)[c]
1	[Rh(COD)((*R*)-BINAP)][SbF_6]	–	H_2O	90	<5
2	[Rh(COD)((*R*)-BINAP)][SbF_6]	–	Dioxane, K_3PO_4	92	<5
3	[RhCl(COD)]$_2$	(*S*)-BINAP	Dioxane, K_3PO_4	93	10
4	[Rh(OH)(COD)]$_2$	(*R*)-BINAP	Dioxane, K_3PO_4	97	13
5	[Rh(OH)(COD)]$_2$	(*R*)-BINAP	Dioxane-H_2O (10:1), NaF	96	<5
6	[Rh(acac)(C_2H_4)$_2$]	(*R*)-BINAP	Dioxane-H_2O (10:1), NaF	<5	–
7	[Rh(COD)(***R,R,R***)-**179**)][SbF_6]	–	Dioxane, K_3PO_4	93	<5
8	[Rh(OH)(COD)]$_2$	(***R,R,R***)-**179**	Dioxane, K_3PO_4	97	<5
9	[Rh(OH)(COD)]$_2$	(***R,R,R***)-**179**	Dioxane-H_2O (10:1), NaF	6	7
10	[Rh(acac)(C_2H_4)$_2$]	(***R,R,R***)-**179**	Dioxane-H_2O (10:1), NaF	33	<5

[a] Typical reaction conditions: enamide (0.5 mmol), boronic acid (2 mmol), NaF (1.5 mmol), [Rh] (3 mol%), ligand (3.3 mol%), dioxane (1.5 mL), H_2O (150 μL), 100°C, 24 hours; [b] Isolated yield after flash chromatography; [c] Determined by HPLC analysis using a chiral column (Chiralpak AD or Chiralcel OD (10% 2-PrOH:Hexane))

To investigate whether the observed low enantioselectivity is a direct result of the product racemising under the reaction conditions, a sample of (*S*)-L-*N*-phthalimidophenylalanine ethyl ester **170b** was subjected to the reaction conditions presented by Reetz, of heating a 1,4-dioxane-water (10:1) solution with sodium fluoride at 100° C for 24 hours. Analysis of the recovered amino acid derivative showed no change to the starting substrate (Scheme 105).



170b
92% ee

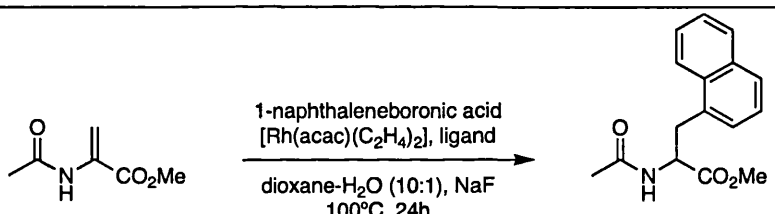
170b
91% ee

Scheme 105 Reaction conditions do not promote racemisation

Better results in terms of enantioselectivity were obtained when using enamide **74**, under the conditions presented by Reetz (Table 10). As reported by Reetz the coupling of phenylboronic acid with **74** using (*R*)-BINAP affords a high yield but no selectivity (Entry 1). However, diphosphite ligand (***R,R,R***)-**179** afforded the desired product **75a** in

excellent yield and high enantioselectivity 92% and 72% respectively (Entry 2). The enantioselectivities obtained under optimised conditions were repeatable and as would be expected, the use of the opposite enatiomer of ligand **(*S*,*S*,*S*)-179** afforded a reversal in the sense of asymmetric induction (Entry 3). Disappointingly, sulphonamide-phosphonite ligand **(*R*)-181** was inactive giving a very low yield of 6% with a similarly low selectivity (10% ee) (Entry 4). The collection of phosphoramidite ligands **183a-c** gave varying results. The least bulky **(*R*)-183a** afforded the product in the highest yield (75%) but with low enantioselectivity (17% ee) (Entry 5). However, the bulkier 3,3'-dibromo-5,5',6,6',7,7',8,8'-octahydro-1,1'-bi-2-naphthol based ligand **(*R*)-183c** gave a lower yield with 42% but an increase in enantioselectivity to 30% ee (Entry 7). Enlargement of bulk at the 3,3' position by the application of **(*S*)-183b** had the effect of completely hindering the reaction. It can therefore be assumed that whilst extra bulk in the 3,3' positions on BINOL has an incremental effect on the enantioselectivity of the reaction, the catalytic activity suffers as a consequence.

Table 10 Ligand effect on the synthesis of amino acid derivatives from **74**[a]



74 **75a**

Entry	Ligand	Yield (%)[b]	ee (%)[c]
1	**(*R*)-BINAP**	81[d]	<5
2	**(*R*,*R*,*R*)-179**	92	72 (*S*)
3	**(*S*,*S*,*S*)-179**	91	71 (*R*)
4	**(*R*)-181**	6	10 (*S*)
5	**(*R*)-183a**	75	17 (*R*)
6	**(*S*)-183b**	0	–
7	**(*R*)-183c**	42	30 (*R*)
8	**(*R*)-183a+(*R*)-183c**	56	22 (*R*)

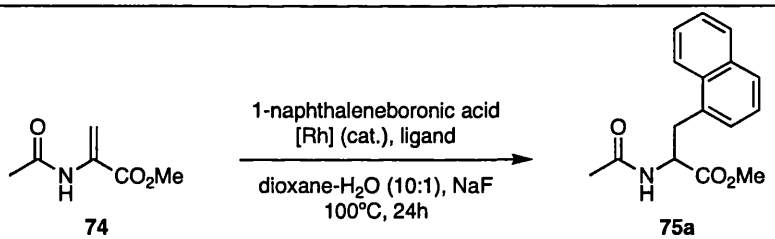
[a] Typical reaction conditions: enamide (0.5 mmol), boronic acid (2 mmol), NaF (1.5 mmol), [Rh(acac)(C2H4)2] (3 mol%), ligand (3.3 mol%), dioxane (1.5 mL), H2O (150 μL), 100°C, 24 hours; [b] Isolated yield after flash chromatography; [c] Determined by HPLC analysis using a chiral column (Chiralpak AD (10% 2-PrOH:Hexane)); [d] phenylboronic acid used instead of 1-naphthalene

Recently a number of research groups have highlighted the beneficial effects of mixing two sterically different monophosphine ligands in one reaction.[67,155] Encouraged by these results the mixed ligand system of **(*R*)-183a/(*R*)-183c** was investigated (Entry 8).

However, rather than observing a significant shift in activity as reported by Feringa,[67] the two ligands appeared to perform as before with the activity and selectivity observed an average of the two individual results. This may indicate that rather that obtaining a mixed ligand set on the rhodium, as reported, there were two distinct rhodium centres each with *like* ligands; or that, coincidently, the mixed system gives an average of the two independent values.

It is noteworthy that the rhodium source had a significant influence on the enantioselectivity and reactivity observed (Table 11). Pertinent to this is the activity of the rhodium source in the absence of ligand (Entries 6-9). The highest enantioselectivities resulted from the use of rhodium salts with substitutionally labile alkenes coordinated, such as $[Rh(acac)(C_2H_4)_2]$ and $[RhCl(COE)_2]_2$ (Entries 1 and 2), which are ineffective in the absence of added ligand. NMR experiments indicate that ligand exchange, ***(R,R,R)*-179** for $(C_2H_4)_2$, is complete within 10 minutes at 25°C (^{31}P NMR shift from δ 145.8 (s) to δ 140.2 (d, J = 308.6 Hz)), whereas the exchange of COD is slower at around 15-20 minutes (^{31}P NMR shift from δ 145.8 (s) to δ 135.7 (d, J = 320.8 Hz)). It is proposed that the increased activity of $[RhCl(COD)]_2$ and $[Rh(OH)(COD)]_2$ (Entries 8 and 9) results in an increased proportion of racemic product, hence the reduction in the overall enantioselectivity observed.

Table 11 Effect of rhodium source on the synthesis of amino acid derivatives from **74**[a]



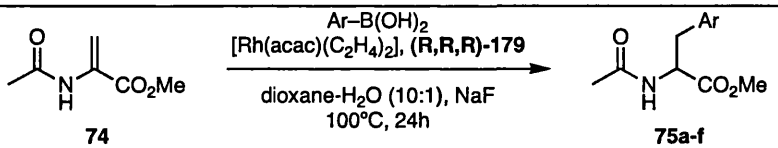
74 **75a**

Entry	Rhodium Source	Ligand	Yield (%)[b]	ee (%)[c]
1	$[Rh(acac)(C_2H_4)_2]$	***(R,R,R)*-179**	92	72
2	$[RhCl(COE)_2]_2$	***(R,R,R)*-179**	98	70
3	$[RhCl(COD)]_2$	***(R,R,R)*-179**	98	50
4	$[Rh(OH)(COE)_2]_2$	***(R,R,R)*-179**	66	69
5	$[Rh(OH)(COD)]_2$	***(R,R,R)*-179**	67	36
6	$[Rh(acac)(C_2H_4)_2]$	–	2	–
7	$[RhCl(COE)_2]_2$	–	2	–
8	$[RhCl(COD)]_2$	–	43	–
9	$[Rh(OH)(COD)]_2$	–	30	–

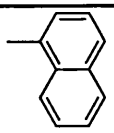
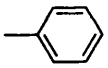
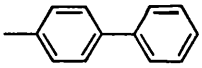
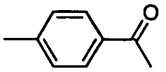
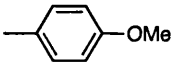
[a] Typical reaction conditions: enamide (0.5 mmol), boronic acid (2 mmol), NaF (1.5 mmol), [Rh] (3 mol%), ***(R,R,R)*-179** (3.3 mol%), dioxane (1.5 mL), H_2O (150 μL), 100°C, 24 hours; [b] Isolated yield after flash chromatography; [c] Determined by HPLC analysis using a chiral column (Chiralpak AD or Chiralcel OD (10% 2-PrOH:Hexane))

From the preceeding results, the favoured precatalyst/ligand combination was determined to be $[Rh(acac)(C_2H_4)_2]$/(***R,R,R***)-**179**. Using the preferred conditions the scope of the reaction was explored with respect to the boronic acid (Table 12). In all cases the products were achieved in good yields, with modest but significant enantioselectivity. Of note is the ability to successfully couple both electron rich and electron deficient boronic acids, with diphosphite ligand (***R,R,R***)-**179**. This is in direct contrast to the use of BINAP which is known to effect the hydrolysis of electron rich arylboronic acids at 100°C.[75]

Table 12 Synthesis of amino acid derivatives from **74**[a]



74 **75a-f**

Entry	Ar	Product	Yield (%)[b]	ee (%)[c]
1		**75a**	92	72 (*S*)
			71[d]	71 (*S*)
2		**75b**	77	55 (*S*)
3		**75c**	79	48 (*S*)
4		**75d**	36	37 (*S*)
5		**75e**	73	56 (*S*)

[a] Typical reaction conditions: enamide (0.5 mmol), boronic acid (2 mmol), NaF (1.5 mmol), $[Rh(acac)(C_2H_4)_2]$ (3 mol%), (***R,R,R***)-**179** (3.3 mol%), dioxane (1.5 mL), H_2O (150 μL), 100°C, 24 hours; [b] Isolated yield after flash chromatography; [c] Determined by HPLC analysis using a chiral column (Chiralpak AD or Chiralcel OD (10% 2-PrOH:Hexane)); [d] 2.5 equivalents of boronic acid used with no NaF

3.6 CONCLUSIONS

In summary the scope of the rhodium-catalysed 1,4-conjugate addition of boronic acids to activated alkenes, has been extended to allow the efficient preparation of unnatural α-amino acids. The use of enantiomerically pure diphosphite ligands has further extended this methodology to allow the preparation of enantio-enriched α-amino acids. The enantioselectivity is sensitive to the choice of rhodium pre-catalyst and key structural elements of the enamide substrate. Comparison with the work of Reetz indicates an

increase in selectivity using a simple BINOL based modular ligand, thus it is proposed that further modification of the ligand backbone should increase the facial selectivity of the dehydroamino acid and with it the enantioselectivity. Furthermore, increased selectivity is envisaged by investigation into a variety of proton sources for the protonation step of the mechanism.

CHAPTER FOUR:

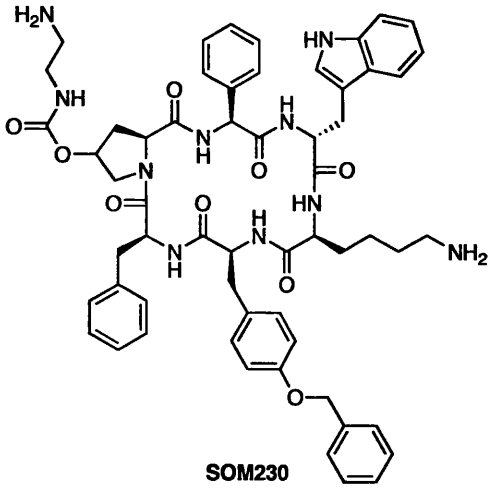
Application of the Rhodium-Catalysed Conjugate Addition Reaction to the Synthesis of Dipeptides

4 Application of the Rhodium-Catalysed Conjugate Addition Reaction to the Synthesis of Dipeptides

4.1 INTRODUCTION

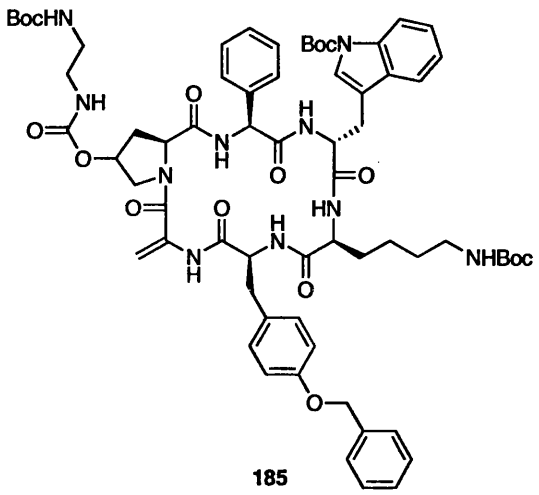
Whilst the synthesis of amino acids *via* the rhodium catalysed conjugate addition of boronic acids is interesting and useful for the rapid synthesis of a diverse range of phenylalanine derivatives. The real advantage of this system comes not from the simple application as a means to generate novel amino acids but the ability to effect a significant structural variation within a larger molecule. For example, typically, if one wanted to synthesise multiple variations of a *pseudo*-peptide structure classically it would be necessary to perform a protracted multi-step synthesis for each variation desired. However this system enables the variation to be effected at, possibly, the final step of a single synthetic procedure.

The cyclohexapeptide somatostatin mimic **SOM230**, has recently been highlighted as exhibiting unique high-affinity binding to human somatostatin receptors (subtypes sst1-sst5), with long-lasting inhibitory effects on growth hormone and insulin-like growth factor-1 release.[157]



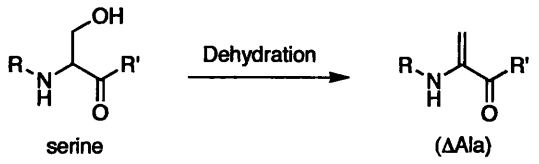
SOM230

Further investigation concerning the effect of introducing functionality to the phenylalanine residue could be envisaged by the application of the rhodium catalysed conjugate addition to the dehydroalanine containing cyclohexapeptide **185**.



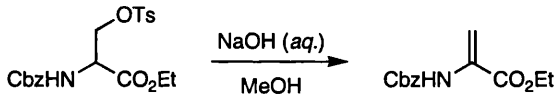
185

The dehydroalanine moiety is itself an interesting peptide subunit, found in a number of naturally occurring biologically active peptides and as such is the focus of a number of synthetic research groups.[158] Although there are examples of the direct peptide coupling of dehydroalanine derivatives[159,160] the procedures are often low yielding, possibly due to polymerisation and hydrolysis of the products.[161] A further draw back is that coupling is only possible at the *C*-terminal due to tautomerisation of the enamine to an imine when the amine is unsubstituted,[162] restricting the diversity of molecules in which the unit is inserted prior to activation. Thus, typically, the dehydroalanine (ΔAla) residue is formed *in situ*, by the dehydration of serine (Scheme 106).



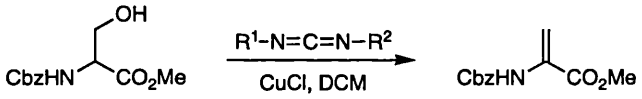
Scheme 106

This section aims to highlight a selection of the methods available for the synthesis of dehydroalanine (ΔAla) derivatives. Photaki reported the β-elimination of *O*-tosylated serine derivatives under the action of base to generate the analogous dehydroalanine derivative (Scheme 107).[163] Similarly, the reaction can be performed with *O*-mesylates[164] and *O*-diphenylphosphates.[163]



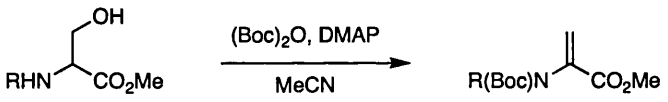
Scheme 107

The reaction of serine derivates with carbodiimides in the presence of 30 mol% copper(I) chloride also enables the β-elimination to proceed (Scheme 108).[165] A variety of carbodiimides have been reported to be active, forming an isourea intermediate which β-eliminates to afford the desired dehydroamino acid and the corresponding urea. The use of the water-soluble carbodiimide (1-cyclohexyl-3-(2-morpholinoethyl)-carbodiimide metho-*p*-toluenesulphonate) eliminates the need for purification by chromatography, due to it's removal during an aqueous work up, resulting in a very simple and attractive method for the synthesis of dehydroalanine derivatives.



Scheme 108

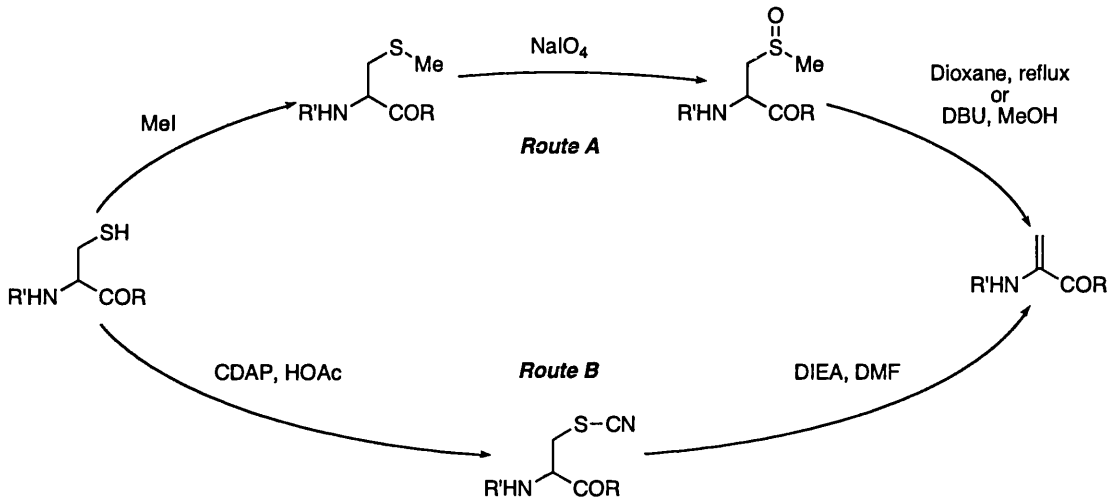
Maia has published the efficient synthesis of dehydroamino acid analogues through the reaction of serine with *tert*-butylpyrocarbonate $(BOC)_2O$, in the presence of DMAP.[161,166] During the course of the reaction all amine protons are substituted by a *tert*-butyloxycarbonyl (Boc) group (Scheme 109).



Scheme 109

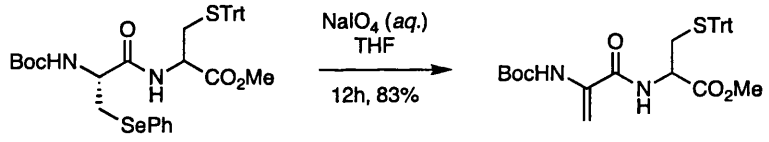
Cysteine has also been shown to undergo β-elimination to form the dehydroamino acid moiety. Two methods dominate this transformation; both involve the conversion of the thiol into a leaving group followed by β-elimination (Scheme 110). Route A[167] utilises the sulphoxide for elimination, in a three step procedure: methylation; oxidation and β-elimination. Performed in organic solvents or organic-aqueous mixtures this route enables the transformation of water insoluble peptides. Route B,[168] however involves the cyanation of the thiol with 1-cyano-4-dimethylaminopyridium tetrafluoroborate

(CDAP) in an aqueous acetic acid solution, followed by β-elimination with di*iso*propylethylamine. The main difference between these methods is the alkylation conditions, with the former performed under basic conditions and the latter under acidic.



Scheme 110

Further methodology used to effect the production of dehydroamino acids include: Horner-Emmons,[169] Methylenation[143] and the oxidative elimination from the unnatural amino acid (*Se*)-phenylselenocysteine (Sec(Ph)) (Scheme 111).[170]

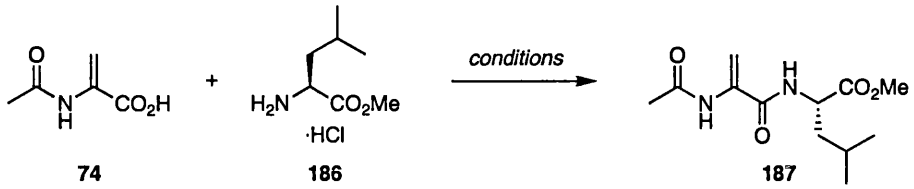


Scheme 111

4.2 SYNTHETIC RESULTS

Exploratory investigations focused on the plausibility of the rhodium catalysed conjugate addition to dipeptides containing the ΔAla residue, with primary research studying the synthesis and addition to Ac-ΔAla-Leu-OMe **187**. It was envisaged that the coupling of the commercially available 2-acetamidoacrylic acid **74** with L-leucine methylester hydrochloride **186** would furnish the desired dipeptide in high yield (Scheme 112). However, although a variety of standard peptide coupling reagents were

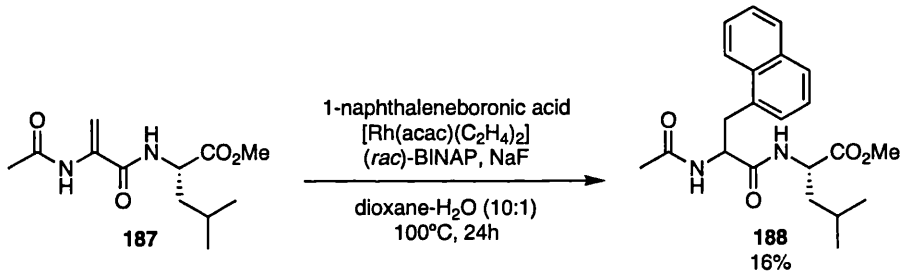
assessed the highest yield obtained was 13% using *N,N'*-dicyclohexylcarbodiimide (DCC) and triethylamine in an ethyl acetate-chloroform solution.[160]



74 186 187

Scheme 112

For the preliminary reactions with the enamide-dipeptide **187** (*rac*)-BINAP was used as the ligand for the rhodium catalysed conjugate addition. Surprisingly, upon exposing **187** to the optimised conditions for the 1,4-addition with 1-naphthaleneboronic acid a single diastereomer of dipeptide **188** was isolated from the reaction mixture by silica gel chromatography in 16% yield (Scheme 113). The low yield of the reaction was attributed to the presence of the amide-activating group of the alkene rather than an ester, a trend reported by Miyaura.[81,82] The observed formation of a single diastereomer was ascribed to the formation of matched and mis-matched pairs when the enamide was coordinated to the rhodium centre.

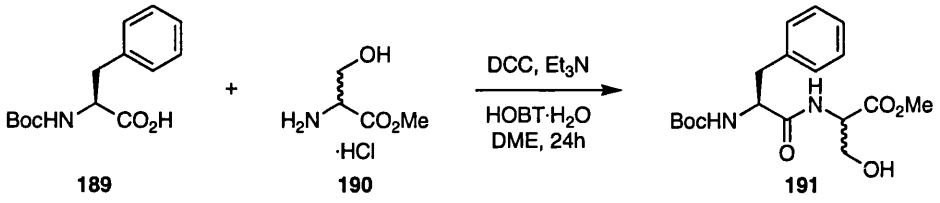


187 **188** 16%

Scheme 113

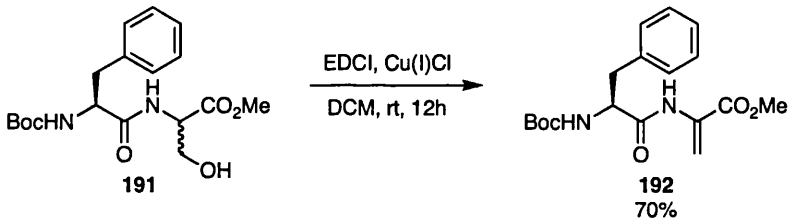
To further investigate the effect of extra bulk on either side of the enamide, and confirm whether the low yield was a likely result of the amide-activating group for the alkene, dipeptide Boc-Phe-ΔAla-OMe **192** was prepared. Due to the instability of the free aminoacrylate and the problems associated with the direct coupling to afford the dipeptide, **192** was prepared in two steps. The coupling of L-*N*-Boc-phenylalanine **189** with D,L-serine methyl ester hydrochloride **190** to generate dipeptide **191** was achieved

in highest yield (49%) by the use of DCC, HOBT·H_2O and Et_3N in a DME solution (Scheme 114).



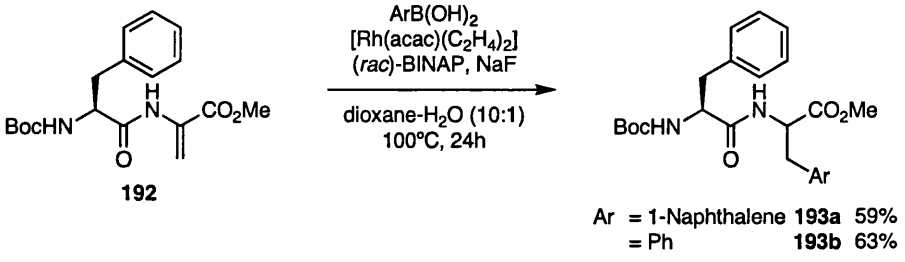
Scheme 114

Acrylate **192** was subsequently obtained in 70% yield from **191** by Miller's method for dehydration using the water soluble carbodiimide EDCI and CuCl (Scheme 115).[165]



Scheme 115

Reaction of **192** with 1-naphthalene- and phenylboronic acid under the optimised conditions for the rhodium-catalysed 1,4-addition, afforded the desired products **193a** and **193b** in 59% and 63% respectively (Scheme 116). Both diastereomers were isolated from the reaction mixtures in a 50:50 ratio. The increased isolated product yield for **193a** and **193b** is suggestive that the acrylamide group of **187** was deactivating the alkene resulting in the lower yield of **188**.



Scheme 116

4.3 SUMMARY

Whilst these results form only a preliminary study investigating the efficacy of the rhodium-catalysed conjugate addition, as a means to systematically manipulate compounds containing an α-amino acid moiety, they clearly illustrate the potential of this process. All that remain is for the diastereoselectivity, both the inherent and that which can be imposed, to be further investigated in order to fully appreciate the significance of this important transformation.

CHAPTER FIVE:

Synthesis of N-Aryl Amino Acids

5 Synthesis of N-Aryl Amino Acids

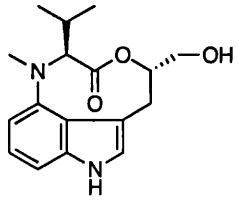
5.1 INTRODUCTION

The success of the rhodium-catalysed conjugate 1,4-addition to protected dehydroamino acids and peptides containing the dehydroalanine residue, encouraged further investigations concerning the range of substrates suitable for the conjugate addition of boronic acids.

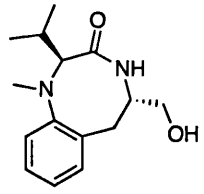
The addition of boronic acids to *N*-aryl-dehydroamino acids would enable the synthesis of a variety of *N*-aryl-α-amino acid moieties, which could be integrated into the synthesis of pharmacologically important structures.

5.2 BACKGROUND

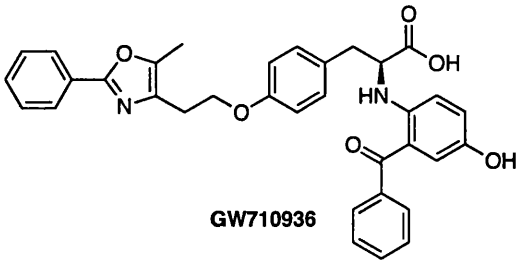
The chiral *N*-aryl-α-amino acid moiety is a common core structure of a number of synthetically challenging and medicinally important agents. These include the protein kinase C (PKC) activators, indolactam-V and it's analogue benzolactame-V8; peroxisome poliferator-activated receptor γ (PPARγ) agonist GW710936X;[171] fibrinogen receptor antagonist SB214857;[172,173] ACE inhibitors[174] and antiulcer agents.[175]



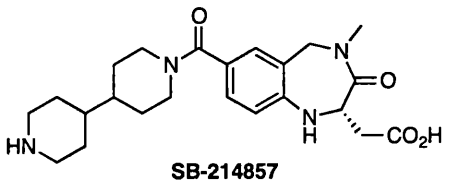
Indolactam-V



Benzolactam-V8



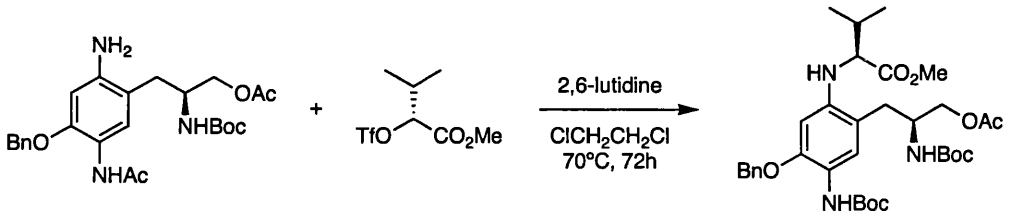
GW710936



SB-214857

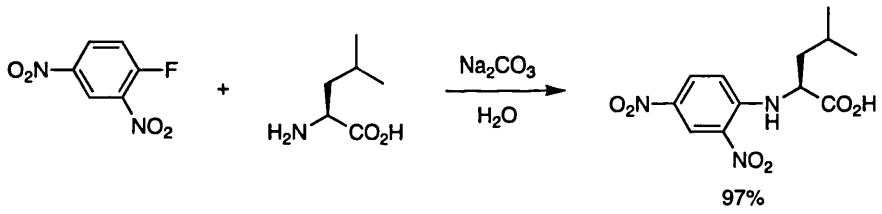
Whilst *N*-aryl amino acids can be synthesised through many of the methods described in Chapter 3.3 the synthesis can often be protracted involving multiple steps. Thus the

development of concise methodologies for the synthesis of *N*-aryl amino acids is of great synthetic use to the organic chemist. Many of the early syntheses of benzolactam-V8 and its analogues utilised S_N2 displacement by coupling anilines with amino acid derived chiral triflates, to form the *N*-aryl amino acid moiety (Scheme 117).[176]



Scheme 117

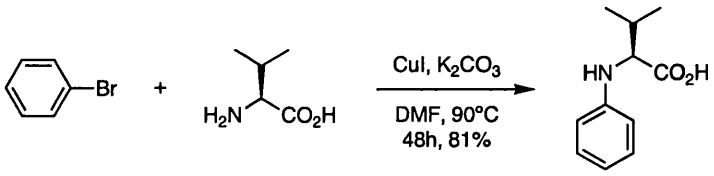
Although the substitution reaction of aryl fluorides with amino acids is a possible route to *N*-aryl amino acids, highly activated systems are required for the S_NAr reaction to proceed efficiently, such as that used by Levy and Chung in the synthesis of 2,4-dinitrophenyl amino acids (Scheme 118).[177]



Scheme 118

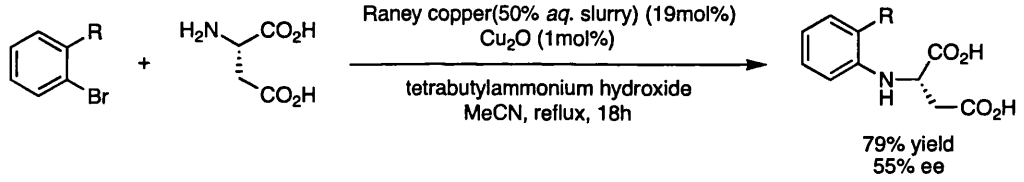
In 1996 Ma and Yao published the palladium-copper-catalysed couplings of chiral α-amino acids with aryl bromides and iodides.[178] Unable to effect the synthesis of the desired *N*-aryl-α-amino acid using Buchwald's and Hartwig's conditions, the addition of catalytic quantities of copper(I) iodide to the reaction mixture generated the desired product. Incorrectly at the time they associated the activity to a duel metallic process in which the copper must be present to activate the amino acid, whilst the palladium performed the *N*-arylation. Subsequent publications, however, detailed the successful synthesis of *N*-aryl amino acids catalysed solely by copper(I) iodide (Scheme 119).[179] During their studies Ma *et al.* noted the reaction proceeded more efficiently when the amino acid possessed a hydrophobic side chain. Indeed, in the absence of a side chain

(glycine) or when a hydrophilic sides chain are present (serine or glutamic acid) no coupling products were observed.



Scheme 119

Later work by Hayes and co-workers highlighted the possibility of coupling aryl bromides with aspartic acid in an aqueous acetonitrile system. A mixture of Raney copper (19 mol%) mixed with copper (I) oxide (1 mol%) was found to catalyse the reaction most efficiently, however, racemisation of the coupled amino acid was observed (Scheme 120).[173]



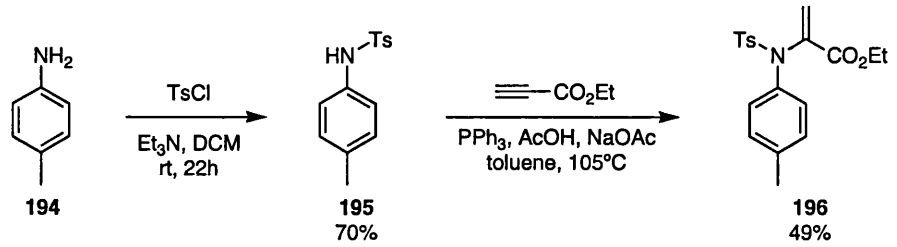
Scheme 120

5.3 RHODIUM-CATALYSED SYNTHESIS OF *N*-ARYL-α-AMINO ACIDS

In collaboration with Miss F. Wood, investigations studying the plausibility of *N*-aryl-amino acid synthesis *via* the rhodium-catalysed 1,4-addition of boronic acids to novel *N*-aryl dehydroalanine derivatives were commenced. In the same publication as the synthesis of ethyl-α-phthalimidoacrylate, Trost additionally reported the addition of *p*-toluenesulphonamide to ethyl phenylpropiolate.[141] It was therefore reasoned that the addition of a *N*-tosylbenzylamine derivates to ethylpropiolate would afford the desired *N*-aryl-α-adduct suitable for the conjugate addition.

4-Methyl-*N*-tosylbenzenamine **195** was prepared, in 70% yield, by the tosylation of 4-methylamine **194** with tosyl chloride, in the presence of triethylamine. Subsequent α-

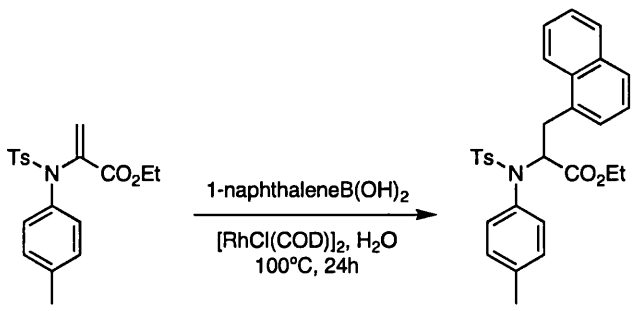
addition to ethylpropiolate afforded the desired *N*-aryl-α-adduct **196** in 49% isolated yield (Scheme 121).



194 **195** 70% **196** 49%

Scheme 121

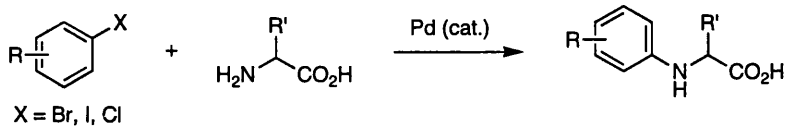
Disappointingly the reaction of **196** with 1-naphthaleneboronic acid under the aqueous conditions reported with ethyl-α-phthalimidoacrylate (Chapter 3.4) failed to yield a significant quantity of the conjugate addition product **197** (Scheme 122). Whilst signals corresponding to the desired product were observed in the ^{1}H NMR, the product co-eluted through flash chromatography with the starting enamide **196**. Efforts to avoid this co-elution through the use of 4-methoxyphenylboronic acid similarly failed to afford the desired product. The modest reactivity observed is rationalised by the increased bulk around the alkene, due to the tosyl protecting group. Whereas the previous enamides tested were relatively planar in configuration, the tetrahedral sulphone group of **196** positions an oxygen toward the metal centre hindering the coordination to the rhodium and the subsequent addition reaction.



196 **197** <3%

Scheme 122

With the rhodium catalysed 1,4-conjugate addition showing few promising results the synthesis of *N*-aryl-α-amino acids was approached from an alternate direction with the palladium catalysed amination reaction of the free α-amino acid (Scheme 123).



Scheme 123 Palladium-catalysed cross coupling of aryl halides with α-amino acids

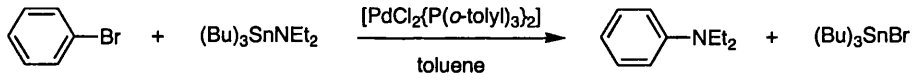
5.4 PALLADIUM-CATALYSED N-ARYLATIONS

One of the most exciting developments in palladium chemistry in recent years is that of the mild and efficient protocol for the catalytic carbon to nitrogen coupling reaction.[117,180]

Buoyed by the results achieved for the application of the hybrid ligands, synthesised in Chapter 2, to the palladium catalysed Suzuki-Miyaura reaction (Chapter 2.6), the application of the ligands to the palladium catalysed amination reaction was also envisaged to be fruitful. To assess the activity of the sulphone-based ligands in the palladium-catalysed amination, initial studies would focus on the coupling of morpholine with halotoluenes. Expansion of this primary work to include the use of commercially available ligands, will examine the arylation of α-amino acids (in the free acid state) as a simple one-pot procedure for the prepare *N*-aryl-α-amino acids.

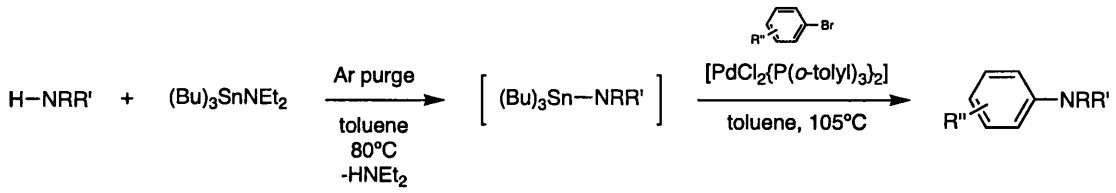
5.4.1 Background

The first palladium-catalysed formation of an aryl C-N bond as reported by Migita and co workers in 1983.[181] The work was analogous to that of Stille, involving electronically neutral aryl bromides and aminotin compounds in the presence of catalytic amounts of $[PdCl_2\{P(o\text{-tolyl})_3\}_2]$ (Scheme 124). This principal discovery was restricted in application by the necessity to use thermally and moisture sensitive tributyltin amides.



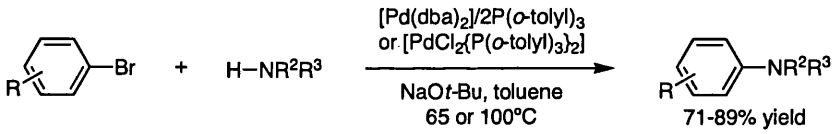
Scheme 124

This methodology was largely ignored until 1994 when Hartwig[182] and Buchwald[130] independently investigated this reaction further. Buchwald reported a procedure in which the tin amide could be generated *in situ* by an amine exchange reaction, enabling a far greater range of amines to be coupled (Scheme 125).



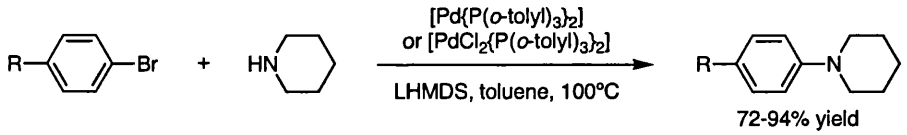
Scheme 125

Further research by these two groups led to the contemporaneous publication in 1995 of tin free methods, by the addition of base. Buchwalds published method involved the use of sodium *tert*-butoxide to deprotonate the reacting amine avoiding the use of aminotin reagents (Scheme 126).[131] The application of the isolated complex $[PdCl_2\{P(o\text{-tolyl})_3\}_2]$, or a catalyst prepared from mixing $[Pd(dba)_2]$ and two equivalents of $P(o\text{-tolyl})_3$, were both reported as active catalysts.



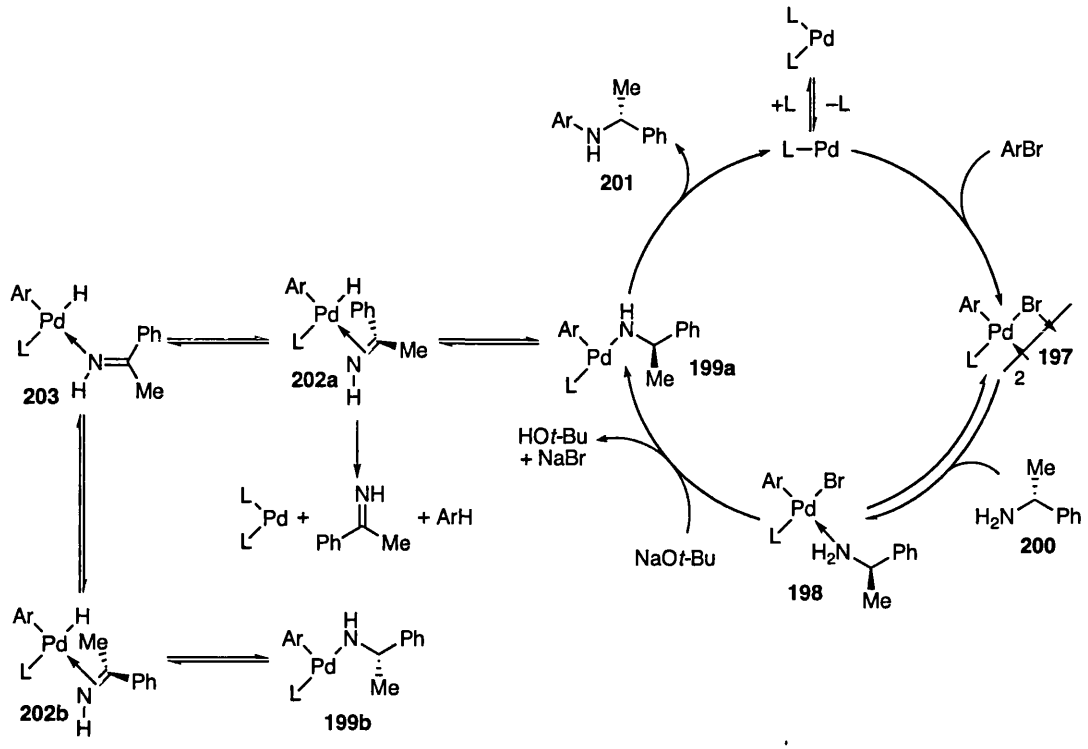
Scheme 126

Similarly Hartwig and Louie reported that lithium hexamethyldisilazane (LHMDS) was an efficient base for such transformations (Scheme 127).[183] $[PdCl_2\{P(o\text{-tolyl})_3\}_2]$ was presented as an active catalyst together with $[Pd\{P(o\text{-tolyl})_3\}_2]$. Both groups later found that an increased activity was realised by the use of bisphosphine ligands.



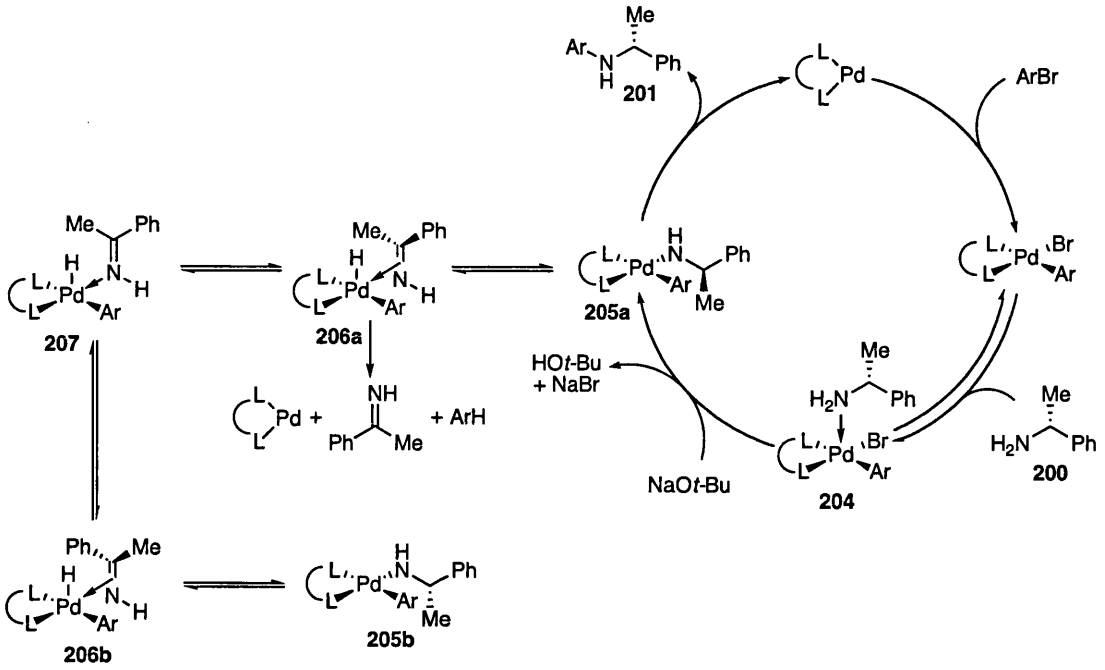
Scheme 127

Buchwald subsequently achieved the coupling of enantiomerically enriched α-substituted amines with aryl bromides using a range of ligands.[138] Whilst monodentate ligands such as P(*o*-tolyl)$_3$ yielded products that were partially or fully racemised, the application of both BINAP and DPPF as ligands afforded the coupled products without an erosion of chirality. A possible explanation for the racemisation focuses on the belief that P(*o*-tolyl)$_3$ favours the formation of mono-phosphine intermediates as the catalytically active species (Scheme 128). Oxidative addition of aryl bromide **200** to the monophosphinated palladium forms a dimeric bromine bridged species **197**, which subsequently forms the monomeric Pd(II) amino complex **198** upon the addition of an amine. Deprotonation generates Pd(II) amido complex **199a**, which can, by reductive elimination, afford the coupled product and regenerate the active palladium species. Alternately, if **199a** possesses β-hydrogens, reversible β-hydride elimination can lead to the formation of imine and protodehalogenated arene, which are common side products in these reactions. Although, β-hydride elimination from complex **199a** initially forms the π-coordinated Pd(II) imine complex **202a**, σ-coordination through the lone pair on the nitrogen is favoured for late transition metals. An equilibrium between the π-coordinated complex **202a** and the σ-coordinated Pd(II) imine complex **203** provides a pathway for the formation of both π-coordinated imine complexes **202a** and **202b** where either face of the prochiral imine is bound to the palladium centre. Migratory insertion of the π-coordinated imine into the palladium-hydride bond, of **202a** and **202b**, leads to the formation of the enantiomeric Pd(II)-amido complexes **199a** and **199b**. Reductive elimination subsequently forms a racemic mixture of coupled product.



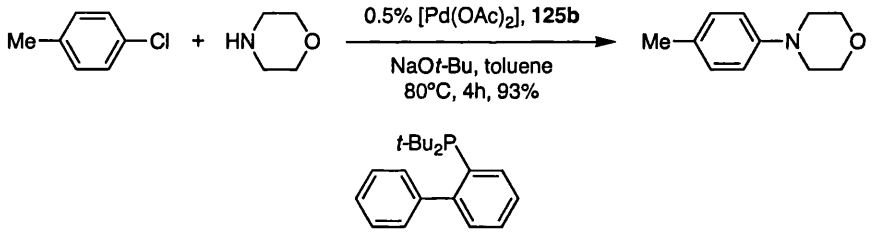
Scheme 128 Possible mechanism for the palladium catalysed amination of aryl bromides with mono(phosphine) ligands

It is believed the use of bisphosphine ligands such as BINAP, increases the steric bulk at the metal, hindering the formation of the σ-coordinated Pd(II)-imine complex **207**. Rotation of the methyl group, in **207**, past the bulky ligand required for racemisation is thus impeded, resulting in the retention of chirality from the starting material (Scheme 129).



Scheme 129 Possible mechanism for the palladium catalysed amination of aryl bromides with a bis(phosphine) ligand

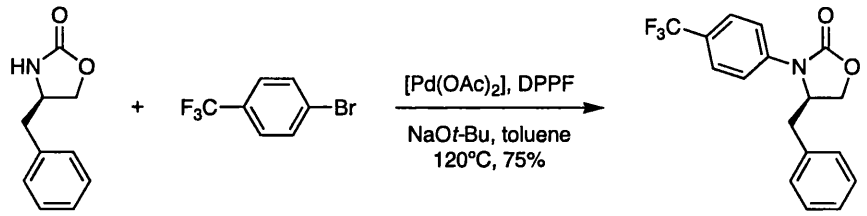
The amination methodology has since progressed, through ligand design, to encompass the coupling to aryl triflates,[184,185] iodides[124,186] and chlorides[124,185] (Scheme 130), with a high level of success, although, generally only the coupling of achiral amines are presented.



125b

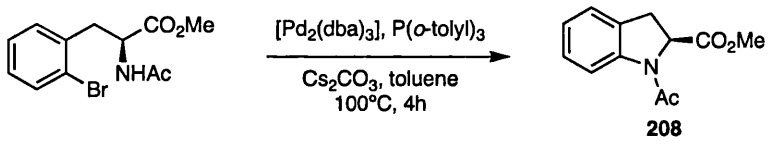
Scheme 130

Since Ma's publications presenting the palladium-copper-catalysed coupling of aryl halides with amino acids, there have been no further publications demonstrating the palladium-catalysed amination of free amino acids. However, it should be noted that the synthesis of *N*-arylated oxazolidinones *via* a palladium catalysed cross coupling has been reported by Madar *et al.* (Scheme 131).[187]



Scheme 131

Buchwald *et al.* have also published the intramolecular coupling of an amino ester to form methyl-1-acetylindoline-2-carboxylate **208**, which is the sole example of the palladium catalysed cross coupling with an α-amino ester to date (Scheme 132).[138]



208

Scheme 132

5.4.2 Palladium-Catalysed Aminations

To assess the efficacy of the sulphone and sulphonamide ligands in the palladium-catalysed amination reaction, halotoluenes **156** were coupled with morpholine **209** in a procedure analogous to that used by Buchwald to measure the effectiveness of biphenyl ligand **125b**.[185] Since the ligands that were synthesised are predicted to behave in a bidentate fashion, it was predicted that a single ligand molecule would be required for each palladium centre in the reaction. Thus the active palladium species was formed *in situ* by the reaction of either $[Pd_2(dba)_3]$ or $[Pd(OAc)_3]$ with the requisite ligand (Pd atom:ligand, 1:1). The reactions were performed using sodium *tert*-butoxide as base in either a sealed pressure tube or schlenk tube under an anhydrous nitrogen atmosphere, with degassed, anhydrous toluene for six hours at 100°C. Table 13 presents the isolated yields of the cross-coupled product **210** obtained using the ligands designed in Chapter 2.

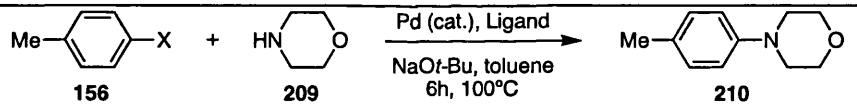
In his earlier work Buchwald noted that triphenylphosphine was an ineffective ligand for the palladium catalysed amination reaction,[130,131] thus it was no surprise that ligand **143** afforded the desired cross coupled product in low yields, given that it is

fundamentally similar to triphenylphosphine. The lack of 4-bromotoluene recovered after the reaction was indicative of protodehalogenation being a major side reaction.

The use of ligand **132** provided us with hope with an isolated yield of 53% obtained with $[Pd(OAc)_2]$ as the palladium source. Interestingly the selectivity of palladium source was reversed for **132** over that with the other ligands tested. No explanation can be offered at this time, however any variation is predicted to be as a result of minor interactions between the ligands and the coordinated species on the palladium salts.

As expected the exchange of the phenyl groups on **132** with the more basic cyclohexyls of **135** and **142** resulted in a substantial increase in catalytic activity. Application of **135** in the reaction with 4-bromotoluene resulted in an isolated yield comparable to that obtained by Buchwald and co-workers using ligand **125b**[185] (93% and 92% respectively). Unfortunately the activity was significantly reduced when applied to the coupling of 4-chlorotoluene, 37% compared to 93% achieved by Buchwald. Whilst the conversion of the cyclohexyl groups of the sulphonamide to the less sterically hindered methyl provided a mild increase in activity (44%) it was not sufficient to challenge the results of Buchwald.

Table 13 Palladium catalysed amination of halotoluenes **156** with morpholine **209**[a]



156 **209** **210**

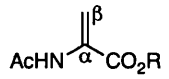
Entry	Ligand	Palladium source	X	Yield (%)
1	**143**	$[Pd_2(dba)_3]$	Br	25
2	**143**	$[Pd(OAc)_2]$	Br	5
3	**143**	$[Pd_2(dba)_3]$	Cl	1
4	**132**	$[Pd_2(dba)_3]$	Br	38
5	**132**	$[Pd(OAc)_2]$	Br	53
6	**132**	$[Pd_2(dba)_3]$	Cl	1
7	**135**	$[Pd_2(dba)_3]$	Br	93
8	**135**	$[Pd(OAc)_2]$	Br	69
9	**135**	$[Pd_2(dba)_3]$	Cl	37
10	**142**	$[Pd_2(dba)_3]$	Br	85
11	**142**	$[Pd(OAc)_2]$	Br	81
12	**142**	$[Pd_2(dba)_3]$	Cl	44
13	**146**	$[Pd_2(dba)_3]$	Br	67

[a] Typical reaction conditions: 1.0 equiv. of aryl halide, 1.2 equiv. of morpholine, 1.4 equiv. of NaO*t*-Bu, 2 mol% Pd, ligand (1:1 Pd), toluene (1mL/mmol halide), 100°C, 6 hours.

Interestingly, ligand **146** provides a significant increase in activity over that achieved with **143**. Given the similarity of the groups around the phosphorous centre this variation is attributed to the increase in rotational freedom of the phenyl groups about

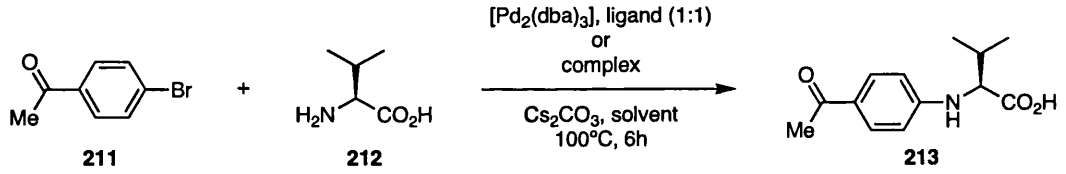
the phosphorus in **146** over those in **143**, and the possibility of a Buchwald like π-interation between the terminal arene ring and the palladium centre.[122]

With these promising results in hand studies progressed to encompass the more challenging arylation of amino acids. Although, the arylation of the analogous amino ester was considered, the greater acidity of the α-hydrogen would lead to an increased risk of the undesired scrambling of chirality. In addition the attempted arylation of dehydroaniline derivatives **74/165** was also dismissed due to the possible Heck addition at the β-position.



R = H **165**
R = Me **74**

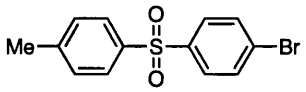
Studies concerning the cross coupling of 4-bromoacetophenone **211** with L-valine **212** catalysed by a range of palladium complexes and ligands in a selection of solvents, generated no appreciable results when caesium carbonate was used as a base (Scheme 133, Appendix 5). The negligible conversions observed were attributed to use of the *weak* base, and the possibility of protodehalogenation occurring, forming acetophenone.



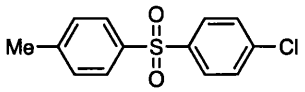
211 **212** **213**

Scheme 133

Previous work within the group, focusing on the Lewis acid catalysed Friedel-Crafts acylation and sulphonylation[188] reactions afforded the activated aryl halides **158a** and **158b**. Given the lack of activity previously observed by Ma and co-workers, in the absence of copper (I) iodide, when studying the cross coupling of aryl halides with amino acids *vide supra* (Chapter 5.2). These sulphones were deemed to be suitably activating, hopefully enabling the synthesis of the corresponding novel *N*-aryl amino acids.

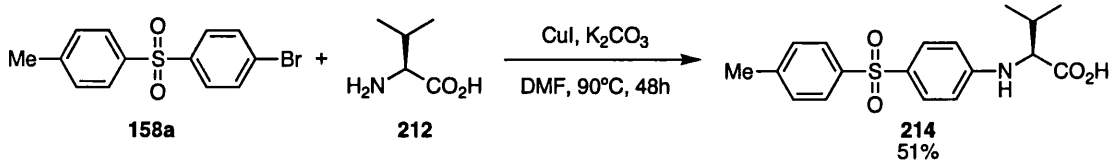


158a



158b

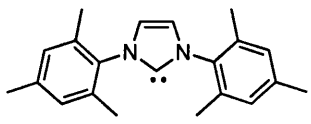
Initial studies of the cross-coupling reaction were predicted to be low yielding. Thus to ensure the conversion of reactions performed by palladium-catalysis could be fully assessed, the coupled product **214** was prepared following the catalytic copper procedure presented by Ma *et al.*[179] Heating a DMF solution of **158a** and **212** with CuI and potassium carbonate generated the desired product in 51% yield (Scheme 134).



158a 212 214 51%

Scheme 134

Table 14 presents selected results for the coupling of 1-bromo-4-tosylbenzene **158a** with L-valine **212**. Primary reactions involved the application of the conditions used for the coupling of bromotoluene with morpholine (treatment of **158a** with **212**, 1mol% $Pd_2(dba)_3$, 2mol% of ligand and sodium *tert*-butoxide in anhydrous toluene at 100°C). Under these conditions, however, no reaction products were observed by NMR analysis, for the commercial ligands PPh_3, $P(t\text{-}Bu)_3$, carbene **215** or BINAP.



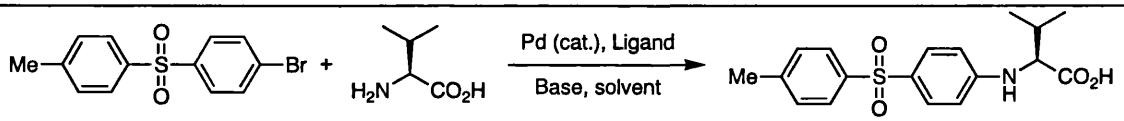
AI

Changing the solvent to anhydrous tetrahydrofuran and the base from the sodium to potassium salt of *tert*-butoxide, whilst heating to reflux at 80°C generated traces of the product, when BINAP was used as the ligand, equivalent to an 8% conversion by NMR analysis. The use of $Pd(OAc)_2$ as the palladium source had no effect on the conversion observed. Interestingly, overheating the solution to 100°C improved the conversion to 19% (Entry 5), which was only marginally decreased by the use of standard laboratory grade tetrahydrofuran (Entry 7).

The conversion was reduced by the use of sodium *tert*-buoxide in tetrahydrofuran, or by the application of aqueous sodium hydroxide (Entries 6 and 11). Surprisingly when dimethylformamide (DMF) was employed as a solvent a significant reduction in activity was realised (Entry 9). It was proposed that upon addition of base to the amino acid the metal ion would coordinate to the acid portion, thus the addition of a crownether could increase the solubility of the amino acid. However, no such effect was observed (Table 14, Entries 2 and 11).

Use of the phase transfer catalyst benzyltriethylammonium chloride (TEBA) with biphasic systems did not aid the reaction, through solubilising the amino acid in the aqueous phase. Although, the use of the weaker base, potassium carbonate, might be partially responsible (Table 14, Entries 8 and 9).

Table 14 Selected results for the palladium catalysed *N*-arylation of L-valine **212**[a]



158a **212** **214**

Entry	Ligand	Solvent	Base	Rxn Time	Additives	Conversion (%)[b]
1	BINAP	Toluene	NaO*t*-Bu	6 h		0
2	BINAP	Toluene	KO*t*-Bu	6 h	18-crown-6	0
3	BINAP	THF	KO*t*-Bu	6 h		8
4	BINAP	THF	KO*t*-Bu	6 h		8[d]
5	BINAP	THF[c]	KO*t*-Bu	6 h		19
6	BINAP	THF[c]	NaO*t*-Bu	6 h		8
7	BINAP	THF(wet)[c]	KO*t*-Bu	6 h		17
8	BINAP	THF/H_2O[c]	K_2CO_3	24 h	TEBA	0
9	BINAP	DMF[c]	NaO*t*-Bu	24 h		<2
10	BINAP	DMF/H_2O[c]	K_2CO_3	24 h	TEBA	0
11	BINAP	THF	Aq. NaOH (5M)	6 h		0
12	BINAP	THF	KO*t*-Bu	16 h	18-crown-6	<2
13	**125a**[e]	Toluene	NaO*t*-Bu	6 h		0
14	**125a**[e]	THF	KO*t*-Bu	6 h		13
15	**125b**[e]	Toluene	NaO*t*-Bu	6 h		6
16	**125b**[e]	THF	KO*t*-Bu	6 h		13
17	[Pd(P*t*-Bu_3)Br]$_2$	Toluene	NaO*t*-Bu	6 h		24
18	**143**	Toluene	NaO*t*-Bu	6 h		26
19	**143**	THF	KO*t*-Bu	6 h		0
20	**132**	Toluene	NaO*t*-Bu	6 h		22
21	**132**	Toluene	NaO*t*-Bu	6 h		14[f]
22	**135**	Toluene	NaO*t*-Bu	6 h		9
23	**135**	THF	KO*t*-Bu	6 h		<3
24	**142**	Toluene	NaO*t*-Bu	6 h		11
25	**142**	THF	KO*t*-Bu	6 h		<5

[a] Typical reaction conditions: 1.0 equiv. of aryl halide, 1.2 equiv. of L-valine, 2.6 equiv. of base, 2 mol% [$Pd_2(dba)_3$], 2 mol% ligand, Anhydrous solvent (1mL/mmol halide), reactions in toluene typically performed at 100°C, reactions in THF typically performed at 80°C; [b] calculated from ^{1}H NMR; [c] The reaction was conducted at 100°C; [d] [$Pd(OAc)_2$] was used in the place of [$Pd_2(dba)_3$]; [e] 4 mol% ligand added (Pd:Ligand, 1:2); [f] arylchloride, **158b**, used in place of the arylbromide **158a**.

Buchwald's biphenyl ligands **125a** and **125b**, highlighted for their increased reactivity in the standard amination reaction, gave disappointingly low results with only 13% conversions achieved for both when the reaction was performed in the same conditions as optimised for BINAP.

Recently Hartwig has presented the use of the palladium (I) tri-*tert*-butylphosphine bromide dimer, $[Pd\{P(t\text{-}Bu)_3\}Br]_2$, as a highly efficient catalyst for the amination reaction.[189] Upon application to our system a 24% conversion was achieved, when reacted in toluene with sodium *tert*-butoxide at 100°C for 6 hours.

Interestingly, contrary to the results with the commercially available ligands the sulphone and sulphonamide ligands prepared above, gave superior results in the toluene system over those in THF (Entries 18-25). To our surprise the highest conversion (26%) was achieved using ligand **143**, which was poorest in the standard amination reaction. The more basic phosphine ligands of **135** and **142**, anticipated to perform better in amination reactions, gave lower conversions at 9% and 11% respectively. The cross-coupling was unexpectedly achieved with aryl chloride **158b** using ligand **132** in 14% conversion.

It should be noted that the conversions presented are solely calculated by comparison of ^1H NMR data, with attempts to isolate the desired products by flash column chromatography and a variety of organic workup procedures failing to yield any significant quantities.

5.5 SUMMARY

In summary the conjugate 1,4-addition of boronic acids to *N*-aryl-dehydroamino acids has been presented with limited success. However, the removal or replacement of the tosyl protecting group for a less sterically bulky group is predicted to enhance activity in this interesting organic transformation.

In addition the sulphone based ligands synthesised in Chapter 2 have been shown to be catalytically active for the palladium catalysed amination reaction of 4-bromotoluene with morpholine. Furthermore, we have presented results displaying the successful *N*-arylation of free amino acids *via* the palladium-catalysed amination reaction.

CHAPTER SIX:

Experimental

6 Experimental

General Considerations

Commercially available solvents and reagents were obtained from Sigma-Aldrich Company Ltd, Lancaster Synthesis Ltd, Fisher Scientific Ltd and Strem Chemicals UK and were used without further purification, apart form the following: dichloromethane and acetonitrile were distilled form calcium hydride, whilst toluene, tetrahydrofuran, hexanes and diethyl ether were distilled from sodium. Solvents and reagents were deoxygenated where necessary by purging with nitrogen. 'Petrol' refers to the fraction of petroleum ether boiling in the range of 40-60°C.

Analytical thin layer chromatography (TLC) was performed using commercially available aluminium backed plates coated with Merck Kieselgel 60 0.20mm (ALUGRAM® sil G/UV_{254}), and visualised under ultra-violet light (at 254 nm), or by staining with potassium permanganate, vanillin or ninhydrin solution. Flash column chromatography was carried out using Merck kieselgel 60 H silica gel (particle size: 0.063-0.100 mm).

Melting points were determined using a Büchi 535 melting point apparatus and are uncorrected. Infra red spectra (4000 to 600cm^{-1}) were recorded on a Perkin Elmer (1600) FT spectrometer with internal calibration. Elemental analyses were performed with an Exeter analytical, INC. CE-440 elemental analyzer in the Chemistry Department at the University of Bath. Fast atom bombardment (FAB) and Electron Impact (EI) mass spectra were obtained using a Fisons VG Autospec Finnigan MAT 8340 instrument at the University of Bath.

^{1}H, ^{13}C and ^{31}P NMR spectra were recorded on a Jeol EX-400, Brüker DPX-300 or a Jeol GX-270 spectrometer. Chemical shifts (δ) are expressed in parts per million (ppm), referenced to an internal $SiMe_4$ standard for ^{1}H-NMR, and relative to solvent for ^{13}C-NMR. The multiplicities of the spectroscopic data are presented in the following manner: apparent (app.) singlet (s), apparent singlet (app. s), broad singlet (br s), doublet (d), doublet of doublets (dd), doublet of triplets (dt), doublet of quartets (dq), doublet of septets (dsep), doublet of multiplets (dm), doublet of doublet of doublets (ddd), triplet (t), triplet of triplets (tt), quartet (q), quintet (qu), septet (sep) and multiplet (m). Coupling constants (*J*) are expressed in Hz. The assignment of aromatic proton resonances for *para* disubstituted benzene rings has been simplified by assuming an AB

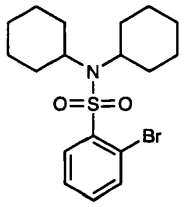
system, however the characteristic features of an AA'BB' system were observed in the NMR spectra.

High Performance Liquid Chromatography (HPLC) was performed on TSP Thermo Separation Products spectra series system, which uses chiral column such as Chiralpak AD by Daicel Chemical Ind. Ltd.

Single crystal X-ray diffraction data was collected on a Nonius Kappa CCD machine. Structure determination and refinement were achieved using the SHELX suite of programmes; drawings were produced using ORTEX or CRYSTALMAKER©.

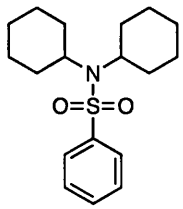
6.1 Ligand Synthesis

2-Bromo-*N,N*-dicyclohexyl-benzenesulphonamide 131



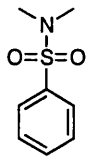
Dicyclohexylamine (145 mg, 0.8 mmol) was taken up in anhydrous dichloromethane (6 mL). To the solution was added 2-bromo-benzenesulphonyl chloride (255 mg, 1 mmol) followed by DMAP (97.7 mg), and triethylamine (506 mg, 5 mmol), and the mixture was heated at reflux for 2.5 hours. The crude product was purified by flash chromatography (dichloromethane) to give a colourless solid (127 mg, 40%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.06-1.30 (6H, m, CH_2), 1.55-1.61 (2H, m, CH_2), 1.67-1.83 (12H, m, CH_2), 3.43-3.51 (2H, m, NCH), 7.33 (1H, dt, J = 5.7, 1.8, Ar), 7.42 (1H, dt, J = 7.8, 1.4, Ar), 7.71 (1H, dd, J = 7.8, 1.4, Ar), 8.17 (1H, dd, J = 7.8, 1.8, Ar).

N,N-Dicyclohexyl-benzenesulphonamide 134



To a stirred solution of benzenesulphonyl chloride (10 g, 56.6 mmol) in dichloromethane (60 mL), at room temperature, was added dicyclohexylamine (36.4 g, 0.2 mol) under an atmosphere of nitrogen. The reaction mixture was allowed to stir for 72 hours, after which it was poured into NaOH (*aq.*) (2 M, 75 mL) and the aqueous layer extracted with dichloromethane (2 × 20 mL). The combined organics were washed with brine (20 mL), dried over magnesium sulfate and concentrated *in vacuo* to yield the crude product. Purification by column chromatography on silica (dichloromethane) gave the title compound (15 g, 83%) as a white solid. R_f (dichloromethane) 0.6; mp 98-99 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.07-1.32 (6H, m, CH_2), 1.57-1.83 (14H, m, CH_2), 3.18-3.28 (2H, m, NCH), 7.43-7.53 (3H, m, Ar), 7.87 (2H, dd, J = 7.8, 1.4, Ar); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 143.1, 131.7, 128.7, 127.0, 58.0, 32.4, 26.5, 25.2; IR ($CDCl_3$, cm^{-1}) ν 2934.4, 2856.0, 1446.0, 1321.4, 1219.0, 1200.1, 11.65.4, 1151.8, 1110.7, 1088.0, 1046.7, 981.4; HRMS (FAB$^+$) calcd for $C_{18}H_{28}NO_2S$ [MH^+]: m/z 321.1763; found: m/z 321.1763; Anal. calcd for $C_{18}H_{27}NO_2S$: C 67.25, H 8.47, N 4.36; found: C 67.70, H 8.53, N 4.30%.

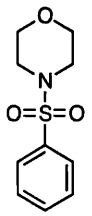
N,N-Dimethyl-benzenesulphonamide 136



Prepared in accordance with the literature procedure.[128]

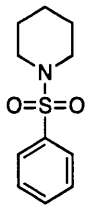
To a solution of benzenesulphonyl chloride (10 g, 56.6 mmol) in tetrahydrofuran (250 mL) at 0 °C, was added dimethylamine (28.4 mL of 40% *aq.*, 226.4 mmol), over 15 minutes. After stirring for 2 hours the solution was diluted with diethyl ether (200 mL) and transferred to a separating funnel, the aqueous layer was extracted with diethyl ether (2 × 50 mL) the combined organics were washed with water (2 × 20 mL) and brine, dried over $MgSO_4$ and evaporated under reduced pressure to afford the title compound in 87% yield (9.12 g) as a yellow solid. R_f (dichloromethane) 0.55; mp 47 °C lit 47.5 °C[190]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.71 (6H, s, CH_3), 7.52-7.64 (3H, m, Ar), 7.79 (2H, dt, J = 6.7, 1.7, Ar); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 135.8, 133.1, 129.4, 128.1, 38.3; IR ($CDCl_3$, cm^{-1}) ν 3013.0, 1445.8, 1343.7, 1229.9, 1211.5, 1196.7, 1165.6, 1091.2, 955.8; HRMS (FAB$^+$) calcd for $C_8H_{12}NO_2S$ [MH^+]: *m/z* 185.0511; found: *m/z* 185.0519; Anal. calcd for $C_8H_{11}NO_2S$: C 51.87, H 5.99, N 7.56; found: C 52.00, H 5.99, N, 7.42%. Data identical to those in the literature.[191]

4-Benzenesulphonyl-morpholine 137



Morpholine (0.99 g, 11.32 mmol) was added to stirred solution of benzenesulphonyl chloride (2.0 g, 11.32 mmol) in dichloromethane (20 mL) at room temperature, followed by the dropwise addition of triethylamine (5.73 g, 56.6 mmol). The resultant mixture was stirred for 2 hours, after which time all the sulphonyl chloride had reacted as judged by TLC, the solution was washed with water (3 × 15 mL), brine and dried over $MgSO_4$, solvents were removed under reduced pressure to afford 2.28 g (89% yield) of the title compound as a white solid. R_f (dichloromethane) 0.29; mp 117 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.00 (4H, t, J = 4.7, CH_2), 3.75 (4H, t, J = 4.7, CH_2), 7.54-7.67 (3H, m, Ar), 7.76 (2H, d, J = 6.9, Ar); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 135.1, 133.1, 129.2, 127.8, 66.1, 46.0; IR ($CHCl_3$, cm^{-1}) ν 3012.1, 2972.0, 2863.7, 1446.1, 1351.0, 1262.0, 1220.0, 1209.1, 1168.8, 1113.4, 1095.7, 1071.0, 946.1; HRMS (FAB^+) calcd for $C_{10}H_{14}NO_3S$ [MH^+]: m/z 227.0616; found: m/z 227.0610; Anal. calcd for $C_{10}H_{13}NO_3S$: C 52.85, H 5.77, N 6.16; found: C 52.80, H 5.87, N, 6.00%.

1-Benzenesulphonyl-piperidine 138



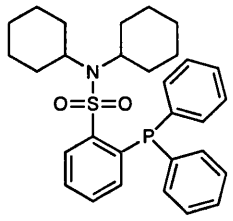
Prepared in accordance to the literature procedure.[129]

Benzenesulphonyl chloride (2.0 g, 11.32 mmol) was slowly added at room temperature to a solution of piperidine (1.9 g, 22.64 mmol) in dry toluene (10 mL). The mixture was stirred for 5 hours, washed with water (3 × 10 mL) and brine, the resultant organics were dried over $MgSO_4$ and evaporated *in vacuo*. Trituation with diethyl ether gave 2.3 g (90% yield) of the title compound, as a white solid. R_f (dichloromethane) 0.62; mp 91 °C, lit 91 °C[129]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.38-1.46 (2H, m, CH_2), 1.61-1.68 (4H, m, CH_2), 2.99 (4H, t, J = 5.5, CH_2), 7.50-7.62 (3H, m, Ar), 7.78 (2H, dd, J = 7.9, 1.4, Ar); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 136.7, 132.9, 129.3, 128.0, 47.32, 25.55, 23.88; IR ($CHCl_3$, cm^{-1}) ν 3013.5, 2943.5, 2854.2, 1445.7, 1341.1, 1230.1, 1218.1, 1211.2, 1201.0, 1171.7, 1164.2, 1151.3, 1093.4, 1051.9, 932.5; HRMS (FAB^+) calcd for $C_{11}H_{16}NO_2S$ [MH^+]: m/z 225.0824; found: m/z 225.0817; Anal. calcd for $C_{11}H_{15}NO_2S$: C 58.64, H 6.71, N 6.22; found: C 58.68, H 6.66, N 6.24%. Data identical to those in the literature.[129]

General procedure for the phosphination of benzene sulphonamides with chlorophosphines

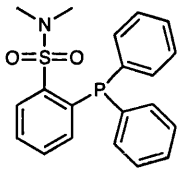
An over dried round-bottomed flask was cooled to room temperature under a nitrogen purge and charged with *N,N*-dialkyl-benzenesulphonamide (15.6 mmol). The flask was purged with nitrogen and tetrahydrofuran (250 mL) was added. The solution was cooled to –78 °C with stirring, and *n*-butyllithium (2.5M in hexanes, 1.1 equiv.) was added dropwise. The solution was stirred at –78 °C for 30min, followed by the dropwise addition of chlorophosphine (19.5 mmol, 1.25 equiv.) in tetrahydrofuran (50mL) to the reaction vessel. The reaction mixture was stirred at –78 °C and allowed to warm slowly to room temperature overnight. After 20 hours the reaction was quenched with saturated NH_4Cl (100 mL), diluted with ether (100 mL), and poured into a separatory funnel. The layers were separated and the aqueous phase was extracted with ether (50 mL). The combined organic layers were dried over anhydrous magnesium sulphate, filtered, and concentrated to give a solid. The crude material was purified by flash chromatography (dichloromethane) to afford the title compound.

N,N-Dicyclohexyl-2-(diphenyl-phosphanyl)-benzenesulphonamide 132



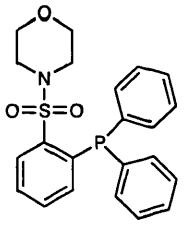
N,*N*-dicyclohexyl-benzenesulphonamide **134** (5.00 g, 15.60 mmol) and chorodiphenylphosphine (3.50 mL, 19.50 mmol) were coupled as stated by the general protocol with *n*-butyllithium (6.85 mL 2.5M in hexanes, 17.12 mmol) to generate the title compound as a colourless solid (34% yield, 2.71 g). R_f (dichloromethane) 0.56; mp 75-78 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.08-1.33 (6H, m, CH_2), 1.56-1.62 (2H, m, CH_2), 1.77 (12H, m, CH_2), 3.61 (2H, m, NCH), 7.04 (1H, m, Ar), 7.18-7.24 (4H, m, Ar), 7.31-7.37 (7H, m, Ar), 7.43 (1H, dt, J = 7.4, 1.4, Ar), 8.07 (1H, m, Ar); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 147.5, 147.2, 137.8, 137.3, 135.7, 133.9, 133.6, 131.5, 129.8, 128.9, 128.5, 128.4, 57.8, 57.7, 33.0, 32.8, 26.6, 25.4; ^{31}P{^{1}H} NMR (121 MHz, $CDCl_3$) δ –5.30 (m); IR ($CHCl_3$, cm^{-1}) 2933.8, 1320.5, 1229.6, 1221.4, 1196.2, 1152.3; HRMS (FAB^+) calcd for $C_{30}H_{37}NO_2PS$ [MH^+]: *m/z* 505.2204; found: *m/z* 505.2215; Anal. calcd for $C_{30}H_{36}NO_2PS$: C 71.26, H 7.18, N 2.77; found: C 70.5, H 6.97, N, 2.54%.

2-(Diphenyl-phosphanyl)-*N,N*-dimethyl-benzenesulphonamide 139



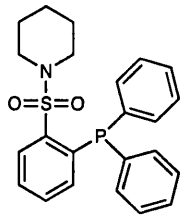
N,N-dimethyl-benzenesulphonamide **136** (666 mg, 3.60 mmol) and choro-diphenylphosphine (808 μL, 4.5 mmol) were coupled as stated by the general protocol with *n*-butyllithium (1.58 mL 2.5M in hexanes, 3.96 mmol) to generate a mixture of the title compound and starting material as an inseparable 1:1 mixture (30% yield, 399 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.62 (6H, s, CH_3), 7.13-7.24 (5H, m, Ar), 7.32-7.35 (6H, m, Ar), 7.42-7.51 (2H, m, Ar), 8.09-8.13 (1H, m, Ar).

4-[2-(Diphenyl-phosphanyl)-benzenesulphonyl]-morpholine 140



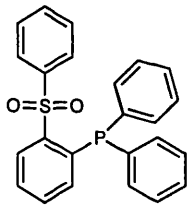
4-Benzenesulphonyl-morpholine **137** (1.00 g, 4.40 mmol) and chorodiphenylphosphine (988 μL, 5.51 mmol) were coupled as stated by the general protocol with *n*-butyllithium (1.94 mL 2.5M in hexanes, 4.84 mmol) to generate an inseparable mixture of the title compound and starting material (35% yield, 634 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.23 (4H, t, J = 4.8, CH_2), 3.61 (4H, t, J = 4.8, CH_2), 7.15-7.24 (5H, m, Ar), 7.32-7.36 (6H, m, Ar), 7.43-7.52 (2H, m, Ar), 8.04-8.08 (1H, m, Ar); ^{31}P{^{1}H} NMR (121 MHz, $CDCl_3$) δ –7.62.

1-[2-(Diphenyl-phosphanyl)-benzenesulphonyl]-piperidine 141



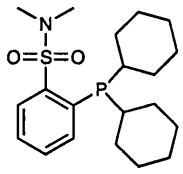
4-Benzenesulphonyl-piperidine **138** (1.00 g, 4.40 mmol) and chorodiphenylphosphine (988 μL, 5.51 mmol) were coupled as stated by the general protocol with *n*-butyllithium (1.94 mL 2.5M in hexanes, 4.84 mmol) to generate an inseparable mixture of the title compound and starting material (27% yield, 489 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42-1.68 (6H, m, CH_2), 3.17-3.20 (4H, t, J = 5.2, CH_2), 7.11-7.60 (13H, m, Ar), 8.03-8.08 (1H, m, Ar); ^{31}P{^{1}H} NMR (121 MHz, $CDCl_3$) δ –7.75.

Diphenyl(2-(phenylsulphonyl)phenyl)phosphine 146



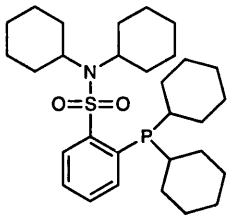
Diphenylsulphone **144** (5.00 g, 22.90 mmol) and chorodiphenylphosphine (5.14 mL, 28.63 mmol) were coupled as stated by the general protocol with *n*-butyllithium (10.07 mL 2.5M in hexanes, 25.20 mmol) to generate the title compound as a colourless solid (48% yield, 4.43 g). R_f (petrol:ethyl acetate 5:1) 0.39; mp 146-149 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.08 (5H, m), 7.27 (5H, m), 7.40-7.56 (6H, m), 8.05 (2H, d, J = 7.2), 8.35 (1H, m); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 145.7, 145.4, 141.8, 138.2, 137.8, 137.0, 136.7, 136.5, 133.7, 133.4, 133.2, 132.9, 130.1, 129.5, 128.7, 128.6, 128.5, 128.4; ^{31}P{^{1}H} NMR (121 MHz, $CDCl_3$) δ –10.65; HRMS (FAB$^+$) calcd for $C_{24}H_{20}O_2PS$ [MH^+]: m/z 403.0922; found: m/z 403.0930;

N,N-dimethyl-2-(dicyclohexyl-phosphanyl)-benzenesulphonamide 142



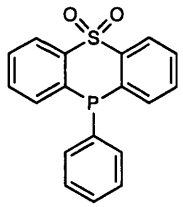
N,N-dimethyl-benzenesulphonamide **136** (1.04 g, 5.60 mmol) and chorodicyclohexylphosphine (1.55 mL, 7.00 mmol) were coupled as stated by the general protocol with *n*-butyllithium (2.64 mL 2.5M in hexanes, 6.20 mmol) to generate the title compound as a colourless solid (75% yield, 1.61 g). R_f (dichloromethane) 0.32; mp 98-100 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.00-1.32 (10H, m), 1.46 (2H, m), 1.65 (4H, m), 1.78 (2H, m), 1.91 (4H, m), 2.83 (6H, s, CH_3), 7.44 (1H, dt, J = 1.1, 7.5, Ar), 7.50 (1H, dt, J = 1.5, 7.5, Ar), 7.70 (1H, d, J = 7.5, Ar), 8.05 (1H, dm, J = 7.5, Ar); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 144.8, 138.5, 135.0, 131.6, 131.0, 128.7, 38.0, 35.9, 30.6, 30.3, 27.7, 27.5, 26.7; ^{31}P{^{1}H} NMR (121 MHz, $CDCl_3$) δ –4.69; ^{1}H{^{31}P} NMR (300 MHz, $CDCl_3$) δ 1.05-1.30 (10H, m), 1.47 (2H, br d, J = 11.1), 1.63-1.66 (4H, m), 1.76-1.80 (2H, m), 1.86-1.94 (4H, m), 2.83 (6H, s, 2xCH_3), 7.45 (1H, app. dt, J = 1.1, 7.6), 7.52 (1H, app. dt, J = 1.1, 7.6), 7.71 (1H, app. dd, J = 1.1, 7.6), 8.05 (1H, app. dd, J = 1.1, 7.6); IR (Nujol, cm^{-1}) ν 1320, 1207, 1151, 1094, 1039, 956, 751, 719, 696; HRMS (FAB$^+$) calcd for $C_{20}H_{33}NO_2PS$ [MH^+]: m/z 382.1970; found: m/z 382.1975.

N,N-dicyclohexyl-2-(dicyclohexyl-phosphanyl)-benzenesulphonamide 135



N,*N*-dicyclohexyl-benzenesulphonamide **134** (1.80 g, 5.60 mmol) and chorodicyclohexylphosphine (1.55 mL, 7.00 mmol) were coupled as stated by the general protocol with *n*-butyllithium (2.64 mL 2.5M in hexanes, 6.16 mmol) to generate the title compound as a colourless foam (73% yield, 2.12 g). R_f (dichloromethane) 0.26; mp 133-135 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.05-1.39 (16H, m), 1.52-1.82 (22H, m), 1.90 (4H, m), 3.62 (2H, m), 7.38 (1H, dt, *J* = 1.5, 7.5, Ar), 7.43 (1H, dt, *J* = 1.5, 7.2, Ar), 7.56 (1H, d, *J* = 7.2, Ar), 8.08 (1H, dm, *J* = 7.5, Ar); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 149.4, 137.8, 137.3, 133.9, 130.5, 128.5, 58.3, 58.3, 35.7, 35.5, 33.5, 30.9, 30.7, 30.2, 30.0, 27.9, 27.8, 27.7, 27.6, 27.1, 26.8, 25.8; ^{31}P{^{1}H} NMR (121 MHz, $CDCl_3$) δ –3.29; ^{1}H{^{31}P} NMR (300 MHz, $CDCl_3$) δ 1.01-1.35 (16H, m), 1.52-1.81 (22H, m), 1.84-1.96 (4H, m), 3.59-3.63 (2H, m), 7.40 (2H, app. qu, *J* = 7.6), 7.56 (1H, app d, *J* = 7.6), 8.08 (1H, app. d, *J* = 7.6); IR (Nujol, cm^{-1}) ν 1322, 1149, 1102, 1049, 980, 893, 850, 818, 752, 723; HRMS (FAB$^+$) calcd for $C_{30}H_{49}NO_2PS$ [MH^+]: *m/z* 518.3222; found: *m/z* 518.3238; Anal. calcd for $C_{30}H_{48}NO_2PS$: C 69.59, H 9.34, N 2.71; found: C 69.30, H 9.29, N 2.52%.

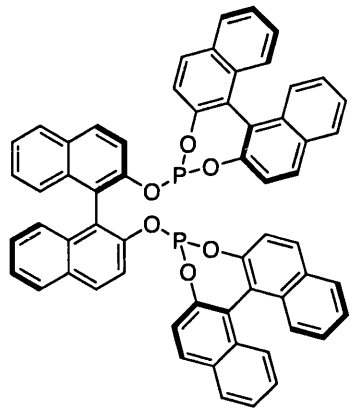
10-Phenyl-10*H*-9-thia-10-phospha-anthracene-9,9-dioxide 143



An over dried round-bottomed flask was cooled to room temperature under a nitrogen purge and charged with diphenylsulphone **144** (5.00 g, 22.91 mmol). The flask was purged with nitrogen and tetrahydrofuran (150 mL) was added. The solution was cooled to –78 °C with stirring, and *n*-butyllithium (20.2 mL 2.5M in hexanes, 50.4 mmol) was added dropwise. The solution was stirred at –78 °C for 30min, then dichlorophenylphosphine (4.51 g, 25.2 mmol) in tetrahydrofuran (100 mL) was added dropwise to the reaction vessel. The reaction mixture was stirred at –78 °C and allowed to warm slowly to room temperature overnight. After 20 hours the reaction was quenched with saturated NH_4Cl (150 mL), diluted with ether (100 mL), and poured into a separatory funnel. The layers were separated and the aqueous phase was extracted with ether (50 mL). The combined organic layers were dried over anhydrous magnesium sulphate, filtered, and concentrated to give a colourless solid. The crude material was purified by flash chromatography (dichloromethane as eluent), followed by recrystallisation from hot ethanol to afford the title compound (5.00 g, 67%) as white prisms. R_f (dichloromethane) 0.59; mp 155-156 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.08 (2H, dt, J = 5.9, 0.7, Ar), 7.37 (2H, tt, J = 7.6, 1.4, Ar), 7.46-7.65 (7H, m, Ar), 8.24 (2H, dt, J = 7.8, 1.5, Ar); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 142.9, 142.6, 138.4, 138.2, 137.7, 137.4, 133.8, 133.6, 131.7, 131.2, 131.2, 131.1, 129.6, 129.5, 128.1, 124.9; ^{31}P{^{1}H} NMR (121 MHz, $CDCl_3$) δ –17.27 (m); IR ($CHCl_3$, cm^{-1}) ν 3012.5, 1577.7, 1445.7, 1436.3, 1311.1, 1292.6, 1255.9, 1216.0, 1209.3, 1202.2, 1197.8, 1159.2, 1130.1, 1109.8, 1038.4; HRMS (FAB$^+$) calcd for $C_{18}H_{13}O_2PS$ [MH^+]: m/z 324.0374; found: m/z 324.0367; Anal. calcd for $C_{18}H_{13}O_2PS$: C 66.66, H 4.04, N 0.00; found: C 66.60, H 4.03, N 0.00%.

See Appendix 1 for selected crystallographic data.

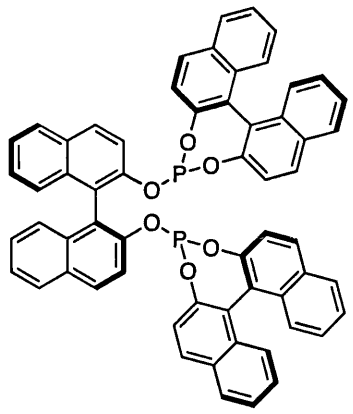
O,O'-(*R*)-(1,1'-dinaphthyl-2,2'-diyl)-(bis-(*O,O'*-(*R*)-(1,1'-dinaphthyl-2,2'-diyl))-phosphite) [*R,R,R*]-179



Prepared in accordance with the literature.[149]

To a cooled solution (–60 °C) of PCl_3 (349 μL, 4 mmol) and triethyl amine (1.67 mL, 12 mmol) in tetrahydrofuran (12 mL) was added (*R*)-BINOL (1.72 g, 6 mmol) in tetrahydrofuran (48 mL). The solution was stirred at –60 °C for 2 h and then allowed to warm to room temperature and stirred for 16 h. The suspension was diluted with tetrahydrofuran and filtered over a plug of celite. After evaporation the residual solid was purified by flash column chromatography (hexanes:dichloromethane, 2:1) yielding the desired diphosphite ligand as a colourless solid in 68% yield (1.25 g). R_f (hexane:dichloromethane, 2:1) 0.37; mp softens 140 melts 168-172 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.52 (2H, d, J = 8.4), 7.16-7.29 (14H, m), 7.32-7.43 (4H, m), 7.51 (2H, d, J = 9.0), 7.73 (2H, d, J = 8.1), 7.79 (2H, d, J = 8.7), 7.83 (2H, d, J = 8.4), 7.90 (2H, d, J = 8.7), 7.97 (2H, d, J = 9.0); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 148.9, 148.0, 147.4, 134.7, 133.1, 132.7, 131.8, 131.5, 131.3, 130.7, 130.5, 130.0, 128.8, 128.6, 128.5, 127.4, 127.4, 127.3, 126.6, 126.5, 126.3, 125.6, 125.4, 125.1, 124.7, 122.8, 122.3, 122.2; ^{31}P{^{1}H} NMR (121.5 MHz, $CDCl_3$) δ 145.83. Data identical to those in the literature.[149]

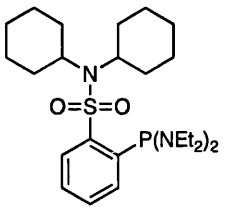
O,O'-(*S*)-(1,1'-dinaphthyl-2,2'-diyl)-(bis-(*O,O'*-(*S*)-(1,1'-dinaphthyl-2,2'-diyl))-phosphite) [*S,S,S*]-179



Prepared in accordance with the literature.[149]

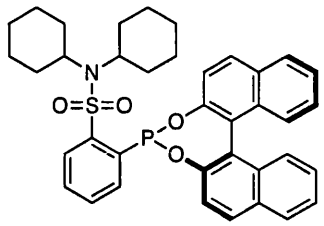
To a cooled solution (–60 °C) of PCl_3 (349 μL, 4 mmol) and triethyl amine (1.67 mL, 12 mmol) in tetrahydrofuran (12 mL) was added (*S*)-BINOL (1.72 g, 6 mmol) in tetrahydrofuran (48 mL). The solution was stirred at –60 °C for 2 h and then allowed to warm to room temperature and stirred for 16 h. The suspension was diluted with tetrahydrofuran and filtered over a plug of celite. After evaporation the residual solid was purified by flash column chromatography (hexanes:dichloromethane, 2:1) yielding the desired diphosphite ligand as a colourless solid in 63% yield (1.15 g). R_f (hexane:dichloromethane, 2:1) 0.37; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.52 (2H, d, J = 8.4), 7.16-7.29 (14H, m), 7.32-7.43 (4H, m), 7.51 (2H, d, J = 9.0), 7.73 (2H, d, J = 8.1), 7.79 (2H, d, J = 8.7), 7.83 (2H, d, J = 8.4), 7.90 (2H, d, J = 8.7), 7.97 (2H, d, J = 9.0); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 148.9, 148.0, 147.4, 134.7, 133.1, 132.7, 131.8, 131.5, 131.3, 130.7, 130.5, 130.0, 128.8, 128.6, 128.5, 127.4, 127.4, 127.3, 126.6, 126.5, 126.3, 125.6, 125.4, 125.1, 124.7, 122.8, 122.3, 122.2; ^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) δ 145.54. Data identical to those in the literature.[150]

N,N-Dicyclohexyl-2-(bis(diethylamino)phosphanyl)-benzenesulphonamide 180



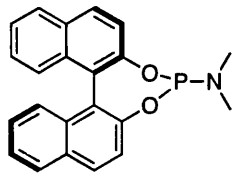
n-Butyl-lithium (7.12 mL of a 2.5M solution in hexane, 17.8 mmol) was added dropwise to a solution of *N,N*-dicylohexyl-benzenesuphonamide **134** (5.20 g, 16.18 mmol) in anhydrous tetrahydrofuran at –78 °C. After the addition the solution was allowed to warm to room temperature for 3 hours prior to being cooled to –78 °C and bis(diethylamino)chlorophosphine (3.74 mL, 17.8 mmol) added dropwise. The reaction mixture was stirred for 3 hours at –78 °C prior to warming to warm to room temperature for 18 hours. After removal of the solvent *in vacuo*, the crude material was dissolved in hexane, filtered and evaporated to dryness under reduced pressure to afford a crude solid which was used in subsequent reactions without further purification (6.41g).

N,N-Dicyclohexyl-2-(*O,O'*-(*R*)-(1,1'-dinaphthyl-2,2'-diyl)-phosphonite)-benzenesulphonamide 181



A solution of *N,N*-dicyclohexyl-2-(bis(diethylamino)phosphanyl)-benzenesulphonamide (1.39 g, 2.81 mmol) and (*R*)-BINOL (805 mg, 2.81 mmol) in toluene (60 mL) was heated at reflux under an atmosphere of nitrogen for 48 hours. After cooling to ambient temperature the residual diethylamine was removed by azeotropic removal through sequential evaporation from toluene (4 × 10 mL) and dichloromethane (2 × 10 mL). To generate the desired product in 99% yield (1.76 g). 80% over two steps from *N,N*-dicyclohexyl-benzenesulphonamide. Mp softens 279, melts 283-284 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12-1.30 (6H, m), 1.61-1.91 (14H, m), 3.49 (2H, app t, J = 10.8), 6.79 (1H, d, J = 8.4). 7.11-7.16 (2H, m,), 7.21-7.26 (2H, m), 7.32-7.47 (4H, m), 7.50 (1H, d, J = 7.6), 7.55 (2H, d, J = 9.2), 7.78 (1H, d, J = 8.0), 7.91-8.01 (3H, m); ^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) δ 166.26; MS (FAB$^+$): *m/z* 636.2 (10%, MH^+); HRMS (FAB$^+$) calcd for $C_{38}H_{39}NO_4PS$ [MH^+]: *m/z* 636.2337; found: *m/z* 636.2333; Anal. calcd for $C_{38}H_{38}NO_4PS$: C 71.79, H 6.02, N 2.20; found: C 71.7, H 6.29, N 2.36%.

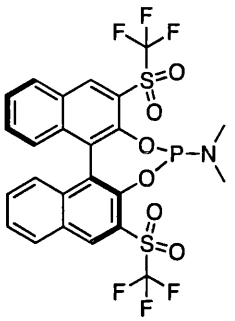
O,O'-(*R*)-(1,1'-dinaphthyl-2,2'-diyl)-*N,N*-dimethylphosphoramidite 183a



Prepared in accordance with the literature procedure.[156]

(*R*)-BINAP (2.0 g, 7.5 mmol), hexamethylphosphorustriamide (1.4 g, 9.5 mmol), NH_4Cl (0.01 g) and 10 mL of dry benzene were heated at reflux temperature for 18 h. The mixture was concentrated under reduced pressure affording a solid which was stirred with 25 mL of dry diethyl ether, filtered and dried under vacuum to give a colourless solid 1.80 g (67%). Mp softens 184-186 °C melts 208 °C, lit 190-191 °C[156]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.54 (6H, d, $J_{H\text{-}P}$ = 9.2), 7.21-7.29 (2H, m), 7.33-7.43 (5H, m), 7.50 (1H, dd, *J* = 0.8, 9.0), 7.89 (2H, d, *J* = 8.8), 7.91 (1H, d, *J* = 8.0), 7.96 (1H, d, *J* = 9.0); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 150.0, 149.4, 132.8, 132.6, 131.3, 130.7, 130.2, 130.0, 128.3, 128.2, 127.0, 126.9, 126.1, 124.7, 124.6, 122.8, 122.7, 122.1, 121.9, 121.9, 36.1, 35.8; ^{1}H{^{31}P} NMR (300 Mhz, $CDCl_3$) δ 2.54 (6H, s), 7.20-7.27 (2H, m), 7.32-7.42 (5H, m), 7.49 (1H, d, *J* = 8.7), 7.88 (2H, d, *J* = 9.0), 7.89 (1H, d, *J* = 8.1), 7.95 (1H, d, *J* = 9.0); ^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) δ 149.62; Optical rotation: $[\alpha]_D^{25}$ –623° (*c*=0.085, $CHCl_3$), lit: (*R*) $[\alpha]_D$ –579° (*c*=0.06, $CHCl_3$)[156]; HRMS (FAB$^+$) calcd for $C_{22}H_{19}NO_2P$ [*MH*$^+$]: *m/z* 360.1153; found: *m/z* 360.1153. Data identical to those in the literature.[156]

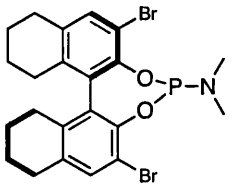
O,O'-(*S*)-(1,1'-dinaphthyl-2,2'-diyl-3,3'-bis-trifluoromethanesulphonyl)-*N,N*-dimethylphosphoramidite 183b



(*S*)-3,3'-Bis-trifluoromethanesulphonyl-[1,1']binaphthalenyl-2,2'-diol (300 mg, 0.55 mmol), hexamethylphosphorustriamide (124 μL, 0.68 mmol), NH_4Cl (1 crystal) and 1 mL of dry benzene were heated to reflux temperature for 18 h. The mixture was concentrated under reduced pressure to afford an oil, purification by flash silica chromatography (petrol:dichloromethane, 2:1) gave a colourless solid 163 mg (48%). R_f (petrol:dichloromethane, 2:1) 0.24; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.58 (6H, br d, J = 5.1), 7.18 (1H, d, J = 8.1), 7.26 (1H, d, J = 8.1), 7.47-7.55 (2H, m), 7.59-7.65 (2H, m), 8.13 (1H, d, J = 7.5), 8.14 (1H, d, J = 7.5), 8.87 (1H, s), 8.89 (1H, s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 138.2, 138.2, 137.4, 136.8, 131.5, 131.5, 131.0, 129.9, 129.7, 129.6, 129.0, 127.5, 127.2, 127.0, 126.9, 125.9, 125.4, 124.9, 124.8, 36 (br s); ^{19}F NMR (376 MHz, $CDCl_3$) δ –76.8 (d, J = 5.3), –76.9 (s); ^{31}P{^{1}H} NMR (121.5 MHz, $CDCl_3$) δ 157.2 (q, J = 5.3); Optical rotation: $[\alpha]_D^{25}$ +541° (c=0.085, $CHCl_3$); HRMS (FAB$^+$) calcd for $C_{24}H_{17}F_6NO_6PS_2$ [MH^+]: m/z 624.0139; found: m/z 624.0148; Anal. calcd for $C_{24}H_{16}F_6NO_6PS_2$: C 46.23, H 2.59, N 2.25, found: C 46.2, H 2.71, N 2.13%.

See Appendix 4 for selected crystallographic data.

O,O'-(*R*)-(1,1'-dinaphthyl-2,2'-diyl-3,3'-dibromo-5,5',6,6',7,7',8,8'-octahydro)-*N,N*-dimethylphosphoramidite 183c

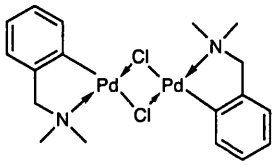


(R)-(+)-3,3'-dibromo-5,5',6,6',7,7',8,8'-octahydro-1,1'-bi-2-naphthol (150 mg, 0.33 mmol), hexamethylphosphorustriamide (75 μL, 0.42 mmol), NH_4Cl (1 crystal) and 1 mL of dry benzene were heated to reflux temperature for 18 h. The mixture was concentrated under reduced pressure to afford an oil, purification by flash silica chromatography (petrol:dichloromethane, 2:1) gave a colourless solid 104 mg (60%). ^1H NMR (400 MHz, $CDCl_3$) δ 1.50-1.58 (2H, m), 1.71-1.81 (6H, m), 2.17 (1H, ddd, J = 4.4, 6.4, 16.8), 2.25 (1H, ddd, J = 4.4, 6.4, 16.8), 2.46-2.59 (2H, m), 2.51 (6H, d, $J_{H\text{-}P}$ = 9.2), 2.77 (4H, ddd, J = 5.6, 6.4), 7.28 (1H, s), 7.33 (1H, s); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 137.5, 137.1, 135.7, 134.7, 132.8, 112.8, 35.8, 35.6, 29.4, 29.2, 28.1, 27.9, 23.0, 22.9, 22.9, 22.7; $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$) δ 141.84; Optical rotation: $[\alpha]_D^{25}$ –461° (c=0.065, $CHCl_3$).

6.2 Transition Metal Complexes: Palladium

Di-μ-chloro-bis(N,N-dimethylbenzylamine-2-C,N)dipalladium(II) from Palladium(II) Dichloride

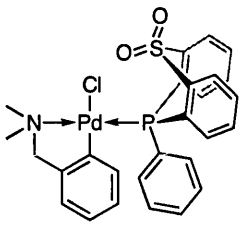
$[Pd(\mu\text{-}Cl)(dmba)]_2$



Prepared in accordance to the literature procedure.[192]

A heterogeneous mixture of *N*,*N*-dimethylbenzylamine (7.35 g, 54 mmol) and palladium(II) dichloride (4.82g, 27.0 mmol), in methanol (270 mL) was stirred at room temperature. After 6 hours, all the palladium dichloride had dissolved and was replaced by a yellow brown crystalline solid. Recrystallisation from boiling benzene-*n*-hexane generated 5.44g (73%) of the title complex as yellow cubes. Mp 174 °C (lit. mp 183-185 °C)[192]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.84 (3H, s, CH_3), 2.87 (3H, s, CH_3), 3.93 (2H, s, CH_2), 6.87 (2H, m, Ar), 6.97 (1H, m, Ar), 7.17 (1H, m, Ar); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 146.9, 146.8, 143.1, 142.9, 133.4, 132.9, 125.2, 124.7, 121.5, 73.3, 73.2, 52.9, 52.6; IR ($CHCl_3$, cm^{-1}) *ν* 3012.0, 1453.8, 1260.3, 1237.9, 1231.9, 1225.7, 1220.1, 1212.0, 1207.1, 2202.2, 1195.7, 1096.0, 1016.0; Anal. calcd for $C_{18}H_{24}Cl_2N_2Pd_2$: C 39.16, H 4.38, N 5.07; found: C 39.25, H 4.33, N 5.00%.

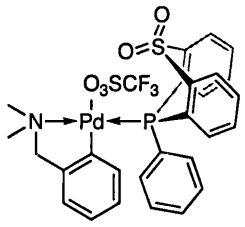
[PdCl(dmba)(10-Phenyl-10*H*-9-thia-10-phospha-anthracene-9,9-dioxide)] 147



10-Phenyl-10*H*-9-thia-10-phospha-anthracene 9,9-dioxide **143** (163 mg, 0.5 mmol) was added to a solution of $[Pd(\mu\text{-}Cl)(dmba)]_2$ (139 mg, 0.25 mmol) in dichloromethane (13 mL) at ambient temperature. The mixture was stirred for 30 min, filtered, and the volatiles evaporated to leave a pale green powder, which was washed with diethyl ether (5 mL) and pentane (2 × 5 mL) and dried under vacuum. Crystallization from dichloromethane-hexane afforded pale green prisms suitable for X-ray diffraction study. Yield 271mg (90%). Mp 207 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.82 (6H, d, $^4J_{P\text{-}H}$ = 2.6, $N(CH_3)_2$), 4.05 (2H, d, $^4J_{P\text{-}H}$ = 2.0, CH_2), 6.10 (1H, t, J = 7.4, Ar), 6.35 (1H, t, J = 7.4, Ar), 6.76 (1H, t, J = 7.1, Ar), 6.92 (1H, d, J = 7.1, Ar), 7.43 (2H, m, Ar), 7.52 (3 H, m, Ar), 7.65 (4H, m, Ar), 8.00 (2H, dd, J = 12.5, 1.5, Ar), 8.24 (2H, dd, J = 7.7, 1.7, Ar); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 151.9, 148.2, 141.7, 137.1, 136.9, 135.4, 135.2, 132.7, 132.1, 131.6, 131.5, 131.2, 128.7, 128.6, 125.4, 125.3, 124.1, 122.6, 73.3, 50.7; ^{31}P{^{1}H} NMR (121 MHz, $CDCl_3$) δ 16.43; ^{1}H{^{31}P} NMR (300 MHz, $CDCl_3$) δ 2.82 (6H, s, CH_3), 4.05 (2H, s, CH_2), 6.11 (1H, d, J = 7.7, Ar), 6.35 (1H, t, J = 7.3, Ar), 6.75 (1H, t, J = 7.3, Ar), 6.92 (1H, d, J = 7.2, Ar), 7.42 (2H, m, Ar), 7.52 (3H, m, Ar), 7.65 (4H, m, Ar), 7.99 (2H, d, J = 7.5, Ar), 8.24 (2H, d, J = 7.7, Ar); IR ($CHCl_3$, cm^{-1}) ν 2962.0, 1719.8, 1453.9, 1314.4, 1261.1, 1236.2, 1229.7, 1222.1, 1215.7, 1212.0, 1202.2, 1195.0, 1189.8, 1164.1, 1099.1, 1015.6; Anal. calcd for $C_{27}H_{25}ClNO_2PPdS$: C 54.01, H 4.20, N 2.33; found: C 53.60, H 4.33, N 2.27%.

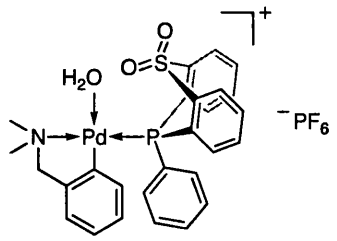
See Appendix 1 for selected crystallographic data.

[Pd(O_3SCF_3)(dmba)(10-Phenyl-10*H*-9-thia-10-phospha-anthracene-9,9-dioxide)] 149



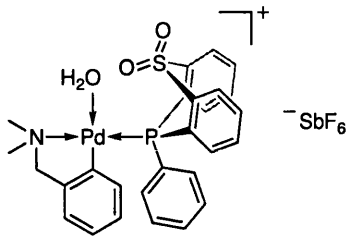
Complex **147** (150 mg, 0.25 mmol), was treated with $Ag[O_3SCF_3]$ (64 mg, 0.25 mmol) in dichloromethane (20 mL) at ambient temperature and stirred for 20 min. The solution was filtered and the solvent was removed under reduced pressure. The residue was washed with pentane (10 mL), crystallization from dichloromethane-hexane generated pale yellow-green prisms suitable for X-ray diffraction study (153 mg, 86%);
mp 206-208 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.74 (6H, d, $^4J_{P-H}$ = 2.9, $N(CH_3)_2$), 3.95 (2H, d, $^4J_{P-H}$ = 1.9, CH_2), 6.54 (1H, t, *J* = 6.7, Ar), 6.63 (1H, t, *J* = 6.7, Ar), 6.81 (2H, m, Ar), 7.42 (4H, m, Ar), 7.58 (4H, m, Ar), 7.74 (1H, m, Ar), 8.05 (2H, dd, *J* = 13.0, 7.4, Ar), 8.23 (2H, dd, *J* = 7.6, 2.9, Ar); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 148.2, 148.2, 141.3, 141.3, 137.4, 137.2, 134.5, 134.4, 133.6, 133.3, 132.7, 131.8, 131.7, 130.8, 130.8, 129.8, 129.7, 125.8, 125.8, 124.9, 123.2, 117.5, 71.8 (d, J_{P-C} = 3), 49.7 (d, J_{P-C} = 2); ^{31}P{^{1}H} NMR (121 MHz, $CDCl_3$) δ 13.29; ^{1}H{^{31}P} NMR (300 MHz, $CDCl_3$) δ 2.74 (6H, s, CH_3), 3.95 (2H, s, CH_2), 6.53 (1H, t, *J* = 6.7, Ar), 6.63 (1H, d, *J* = 7.6, Ar), 6.80 (2H, m, Ar), 7.44 (4H, m, Ar), 7.61 (4H, m, Ar), 7.73 (1H, d, *J* = 7.2, Ar), 8.05 (2H, d, *J* = 7.3, Ar), 8.23 (2H, d, *J* = 7.7, Ar); IR ($CHCl_3$, cm^{-1}) *v* 2963.7, 1452.3, 1438.4, 1313.8, 1260.3, 1234.1, 1221.9, 1212.0, 1203.8, 1193.0, 1185.8, 1164.6, 1108.2, 1016.0; Anal. calcd for $C_{28}H_{25}F3NO_5PPdS_2$: C 47.10, H 3.53, N 1.96; found: C 46.70, H 3.53, N 1.95%.
See Appendix 1 for selected crystallographic data.

[Pd(H$_2$O)(dmba)(10-Phenyl-10*H*-9-thia-10-phospha-anthracene-9,9-dioxide)][PF$_6$] 150



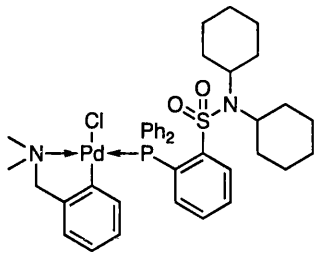
Complex **147** (150 mg, 0.25 mmol), was treated with Ag[PF_6] (63 mg, 0.25 mmol) in dichloromethane (20 mL) at ambient temperature and stirred for 20 min. The solution was filtered and the solvent was removed under reduced pressure. The residue was washed with pentane (10 mL), crystallization from dichloromethane-hexane generated pale green prisms (157 mg, 88%). Mp 168-171 °C (dec); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.70 (6H, d, $^4J_{P\text{-}H}$ = 2.8, $N(CH_3)_2$), 4.01 (2H, d, $^4J_{P\text{-}H}$ = 2.0, CH_2), 6.49 (1H, t, J = 5.4, Ar), 6.56 (1H, t, J = 5.4, Ar), 6.88 (1H, t, J = 5.1, Ar), 6.93 (1H, dd, J = 5.7, 1.2, Ar), 7.54-7.72 (9H, m, Ar), 7.78 (1H, dd, J = 9.9, 0.9, Ar), 7.79 (1H, d, J = 9.9, Ar), 7.27 (2H, ddd, J = 6.0, 2.4, 0.9, Ar); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 148.3, 141.6, 141.0, 140.9, 136.5, 136.3, 136.0, 135.9, 135.3, 135.2, 133.7, 133.2, 133.1, 131.9, 131.5, 130.2, 130.1, 126.5, 126.5, 126.2, 126.2, 125.8, 124.6, 123.9, 71.6, 50.3; ^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) δ 13.47, –142.82 (sep $J_{P\text{-}F}$ = 713, PF_6); IR ($CHCl_3$, cm^{-1}) ν 2963.0, 1314.7, 1260.6, 1238.1, 1230.2, 1217.5, 1208.4, 1202.2, 1193.3, 1171.8, 1108.0, 1036.3, 1012.6; Anal. calcd for $C_{27}H_{25}F_6NO_2P_2PdS{\cdot}H_2O$: C 44.55, H 3.74, N 1.92; found: C 44.6, H 3.75, N 1.89%.

[Pd(H$_2$O)(dmba)(10-Phenyl-10*H*-9-thia-10-phospha-anthracene-9,9-dioxide)][SbF$_6$] 151



Complex **147** (150 mg, 0.25 mmol), was treated with Ag[SbF_6] (86 mg, 0.25 mmol) in dichloromethane (20 mL) at ambient temperature and stirred for 20 min. The solution was filtered and the solvent was removed under reduced pressure. The residue was washed with pentane (10 mL), crystallization from dichloromethane-hexane generated pale yellow-green prisms suitable for X-ray diffraction study (189 mg, 95%). Mp 123 °C softens, changes colour 130 °C melts 168 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.72 (6H, d, $^4J_{P-H}$ = 2.8, $N(CH_3)_2$), 4.03 (2H, d, $^4J_{P-H}$ = 2.0, CH_2), 6.63-6.64 (2H, m, Ar), 6.91-6.98 (2H, m, Ar), 7.53-7.63 (6H, m, Ar), 7.70-7.74, (3H, m, Ar), 7.84 (2H, dd, *J* = 9.9, 6.0, Ar), 8.29-8.32 (2H, m, Ar); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 148.1, 141.4, 140.6, 140.5, 136.7, 134.6, 133.1, 132.9, 132.4, 131.8, 131.5, 130.1, 129.9, 126.1, 126.0, 125.6, 123.7, 123.2, 77.2, 50.0; ^{31}P{^{1}H} NMR (121 MHz, $CDCl_3$) δ 12.82; IR ($CHCl_3$, cm^{-1}) *ν* 2971.8, 1516.5, 1508.1, 1314.3, 1261.3, 1236.0, 1230.0, 1226.1, 1221.5, 1209.2, 1204.0, 1195.4, 1186.0, 1172.0, 1108.4, 1036.3; Anal. calcd for $C_{27}H_{25}F_6NO_2PPdSSb{\cdot}H_2O$: C 39.61, H 3.32, N 1.71; found: C 39.5, H 3.33, N 1.64%.
See Appendix 1 for selected crystallographic data.

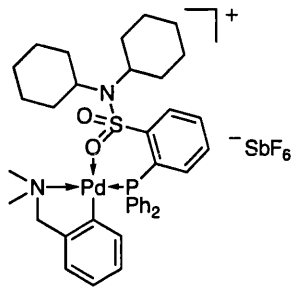
[PdCl(dmba)(*N,N*-Dicyclohexyl-2-(diphenyl-phosphanyl)-benzenesulphonamide)] 152



Ligand **132** (253 mg, 0.5 mmol) was added to a solution of $[Pd(\mu\text{-}Cl)(dmba)]_2$ (139 mg, 0.25 mmol) in dichloromethane (13 mL) at ambient temperature. The mixture was stirred for 30 min, filtered, and the volatiles evaporated to leave a pale yellow powder, which was washed with diethyl ether (5 mL) and pentane (2 × 5 mL) and dried under vacuum. Crystallisation from dichloromethane-hexane afforded pale green prisms suitable for X-ray diffraction study: Yield 359 mg (92%). Mp 170-172 °C softens 198-200 °C (dec); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85 (1H, t, *J* = 6.4), 1.03 (2H, m), 1.27 (4H, m), 1.44-1.84 (13H, m), 2.85 (6H, br s, CH_3), 3.44 (2H, br s, NCH), 3.80-4.40 (2H, br s, CH_2N), 6.31 (1H, t, *J* = 6.8, Ar), 6.40 (1H, t, *J* = 7.5, Ar), 6.83 (1H, t, *J* = 7.2, Ar), 6.98 (1H, d, *J* = 7.2, Ar), 7.06 (1H, ddd, *J* = 1.1, 7.9, 10.9, Ar), 7.29-7.47 (9H, m, Ar), 7.50-8.20 (3H, br m, Ar), 7.91 (1H, ddd, *J* = 1.1, 4.1, 7.9, Ar); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 149.3, 148.4, 144.5, 144.3, 137.8, 137.6, 137.0, 136.4, 134.1, 134.0, 130.7, 130.6, 130.4, 130.1, 130.1, 129.5, 127.9, 124.5, 124.5, 123.7, 122.3, 77.23, 73.4, 56.2, 53.4, 50.5, 34.7, 31.8, 26.0, 25.3; ^{31}P{^{1}H} NMR (121 MHz, $CDCl_3$) δ 46.07; ^{1}H{^{31}P} NMR (300 MHz, $CDCl_3$) δ 0.85 (1H, t, *J* = 7.3), 1.03 (2H, m), 1.28 (4H, m), 1.46-1.88 (13H, m), 2.88 (6H, br s, CH_3), 3.45 (2H, br s, NCH), 3.80-4.40 (2H, br s, CH_2N), 6.31 (1H, d, *J* = 6.9, Ar), 6.40 (1H, dt, *J* = 1.1, 7.4, Ar), 6.83 (1H, dt, *J* = 0.8, 7.3, Ar), 6.99 (1H, dd, *J* = 1.1, 7.6, Ar), 7.07 (1H, dd, *J* = 1.1, 8.0, Ar), 7.25-7.47 (9H, m), 7.50-8.20 (3H, br m, Ar), 7.91 (1H, dd, *J* = 1.1, 7.6, Ar); IR (Nujol, cm^{-1}) *ν* 2922, 2857, 2221, 1577, 1558, 1455, 1438, 1406, 1378, 1334, 1311, 1262, 1186, 1151, 1121, 1103, 1095, 1042, 1022, 992, 974, 912, 907, 891, 865, 851, 818, 760, 734, 725; MS (FAB$^+$): *m/z* 745.1 (M – Cl); Anal. calcd for $C_{39}H_{48}ClN_2O_2PPdS{\cdot}H_2O$: C 58.57, H 6.30, N 3.50; found: C 58.2, H 5.97, N 3.38%.

See Appendix 2 for selected crystallographic data.

[Pd(dmba)(*N,N*-Dicyclohexyl-2-(diphenyl-phosphanyl)-benzenesulphonamide)][SbF_6] 153

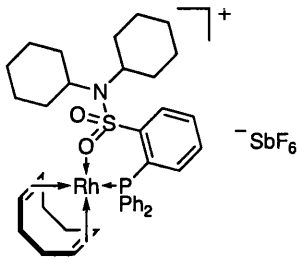


Complex **152** (154 mg, 0.19 mmol), was treated with Ag[SbF_6] (65 mg, 0.19 mmol) in dichloromethane (15 mL) at ambient temperature and stirred for 30 min. The solution was filtered and the solvent was removed under reduced pressure. The residue was washed with pentane (10 mL), crystallization from dichloromethane-hexane generated pale yellow-green prisms suitable for X-ray diffraction study (167 mg, 91%). Mp 179 °C softens, 195 °C decomposes; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86-1.10 (6H, m), 1.48-1.61 (2H, m), 1.62-1.85 (12H, m), 2.85 (6H, d, $^4J_{P-H}$ = 2.7, $N(CH_3)_2$), 2.89-3.06 (2H, m, NCH), 4.09 (2H, s, NCH_2), 5.93 (1H, t, *J* = 7.2, Ar), 6.39 (1H, t, *J* = 7.5, Ar), 6.87 (1H, t, *J* = 7.2, Ar), 6.98 (1H, d, *J* = 6.0, Ar), 7.18 (1H, t, *J* = 9.4, Ar), 7.49-7.63 (10H, m, Ar), 7.69 (1H, t, *J* = 7.5, Ar), 7.84 (1H, t, *J* = 7.7, Ar), 8.02 (1H, dd, *J* = 4.5, 7.2, Ar); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 148.3, 148.2, 143.8, 143.6, 142.4, 136.5, 136.5, 134.9, 133.9, 133.0, 132.7, 132.6, 130.0, 129.8, 129.6, 129.6, 126.0, 126.0, 125.5, 123.6, 70.3 (*J* = 4), 59.3, 50.3 (*J* = 2), 31.8, 29.7, 26.0, 24.7; ^{31}P{^{1}H} NMR (121 MHz, $CDCl_3$) δ 33.40; IR (Nujol, cm^{-1}) *v* 2923, 2854, 2724, 2725, 1583, 1461, 1377, 1293, 1264, 1166, 1140, 1117, 1098, 1042, 1024, 982, 892, 846, 765, 748, 720; MS (FAB^+): *m/z* 745.4 (M – SbF_6); Anal. calcd for $C_{39}H_{48}F_6N_2O_2PPdSSb$: C 47.70, H 4.93, N 2.85; found: C 47.9, H 4.80, N 2.80%.

See Appendix 2 for selected crystallographic data.

6.3 Transition Metal Complexes: Rhodium

[Rh(COD)(*N,N*-Dicyclohexyl-2-(diphenyl-phosphanyl)-benzenesulphonamide)][SbF_6] 155



Ligand **132** (51.3 mg, 0.1 mmol) was added to a solution of chloro-(1,5-cyclooctadiene)rhodium(I) dimer (25 mg, 0.05 mmol) and silver hexafluoroantimonate (35 mg, 0.1 mmol) in dichloromethane (10 mL) at ambient temperature. The mixture was stirred for 30 min, filtered, and the volatiles evaporated to leave a golden powder, which was washed with diethyl ether (5 mL) and pentane (2 × 5 mL) and dried under vacuum. Crystallisation from dichloromethane-hexane produced golden prisms suitable for X-ray diffraction study. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.80-1.06 (6H, m), 1.49 (2H, app d, J = 12.6), 1.58-1.70 (12H, m), 2.01-2.23 (4H, m), 2.49-2.68 (4H, m), 2.70-2.79 (2H, m), 3.30 (2H, s), 5.48 (2H, s), 7.41 (1H, ddd, J = 9.6, 7.8, 1.2), 7.53-7.62 (10H, m), 7.74 (1H, app t, J = 7.5), 7.85 (1H, app t, J = 7.8), 7.97 (1H, ddd, J = 7.8, 4.8, 1.2); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 143.6, 143.5, 134.8, 134.3, 134.0, 133.9, 132.9, 132.3, 130.5, 130.1, 129.8, 129.6, 127.1, 126.5, 109.7, 109.5, 77.2, 72.7, 72.5, 59.2, 32.6, 31.4, 27.9, 25.9, 24.7; ^{31}P{^{1}H} NMR (121 MHz, $CDCl_3$) δ 23.21 (d, J = 149.4).

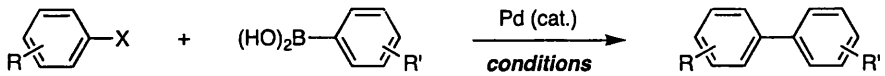
See Appendix 3 for selected crystallographic data.

Bis(η^4-1,5-cyclooctadiene)-di-μ-hydroxo-dirhodium(I) ([Rh(OH)(COD)]$_2$)

Prepared in accordance to the literature procedure.[193]
chloro-(1,5-cyclooctadiene)rhodium(I) dimer (150 mg, 0.30 mmol) in acetone (15 mL) was added to a stirring solution of potassium hydroxide (34 mg, 0.61 mmol) in water (2 mL). After being stirred for 2 hours at room temperature, the yellow suspension is concentrated to ~5 mL. 8 mL of water was added and the solid collected by filtration, and washed with water (10 × 5 mL), vacuum drying over phosphorous(V) oxide, yielded the title compound in 85% yield (116 mg). IR (Nujol, cm^{-1}) ν 3588, 3296, 1324, 1156, 996, 959, 867, 814, 770, 724;

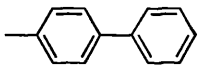
6.4 Suzuki-Miyaura Cross Coupling Reactions

Typical procedure for the palladium-catalysed Suzuki-Miyaura cross coupling



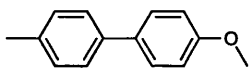
An oven dried Schlenk tube, cooled to room temperature under a nitrogen atmosphere, was charged with aryl halide (1 mmol), Cs_2CO_3 (1.4 mmol), boronic acid (1.5 mmol) [$Pd(OAc)_2$] (20 μmol, 2 mol%), ligand (20 μmol, 2 mol%) and 1,4-dioxane (3 mL). The tube was sealed and heated at 80 °C for 3 hours. The mixture was allowed to cool to room temperature before either being purified directly by flash chromatography (petrol), or filtered through a pad of celite, concentrated, and then purified by flash chromatography to afford analytically pure title compound.

4-Methyl-biphenyl 157



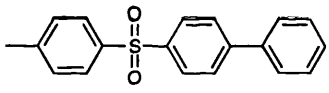
4-Bromotoluene (171 mg, 1 mmol), and phenylboronic acid (183 mg, 1.5 mmol) were coupled under the standard protocol to afford the titled compound as a colourless solid (158 mg, 94%). ^{1}H NMR (300 MHz) δ 2.39 (3H, s, CH_3), 7.25 (2H, d, J = 8.3, Ar), 7.31 (1H, tt, J = 1.8, 7.5, Ar), 7.42 (2H, tm, J = 7.5, Ar), 7.49 (2H, d, J = 8.3, Ar), 7.57 (2H, dm, J = 6.9, Ar); ^{13}C NMR (75.5 MHz) δ 141.1, 138.3, 137.0, 129.5, 128.7, 128.7, 127.2, 127.0, 21.1; IR (film, cm^{-1}) ν 3056, 3027, 2920, 2864, 1948, 1903, 1804, 1659, 1601, 1568, 1519, 1488, 1445, 1403, 1380, 1266, 1217, 1112, 1075, 1038, 1008, 912, 822, 757, 697, 668; HRMS (EI$^+$) calcd for $C_{13}H_{12}$ [M^+]: m/z 168.0939; found: m/z 168.0937. Data identical to those in the literature.[194]

4'-Methoxy-4-methyl-biphenyl



4-Bromotoluene (171 mg, 1 mmol), and 4-methoxyphenylboronic acid (228 mg, 1.5 mmol) were coupled under the standard protocol to afford the titled compound as a colourless solid (197 mg, 99%). Mp 109-110 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.38 (3H, s, CH_3), 3.84 (3H, s, OCH_3), 6.96 (2H, d, J = 9.0, Ar), 7.22 (2H, d, J = 8.5, Ar), 7.45 (2H, d, J = 8.5, Ar), 7.51 (2H, d, J = 9.0, Ar); IR (film, cm^{-1}) ν 3019, 2400, 1610, 1501, 1247, 1215, 1176, 1042, 929, 811, 769, 669; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 160.7, 139.7, 138.1, 135.5, 131.2, 129.7, 128.3, 115.9, 57.0, 22.8; HRMS (EI$^+$) calcd for $C_{14}H_{14}O$ [M^+]: m/z 198.1045; found: m/z 198.1044. Data identical to those in the literature.[195]

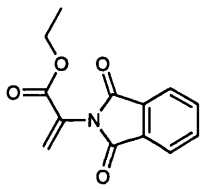
(4-Diphenyl)-*p*-tolyl sulphone 159



(4-Chlorophenyl)-*p*-tolyl sulphone (133 mg, 0.50 mmol), and phenylboronic acid (91 mg, 0.75 mmol) were coupled under the standard protocol to afford the titled compound as a colourless solid (50 mg, 32%). ^{1}H NMR (300 MHz) δ 2.39 (3H, s, CH_3), 7.31 (2H, d, J = 8.3, Ar), 7.39-7.48 (3H, m, Ar), 7.55 (2H, m, Ar), 7.68 (2H, dt, J = 1.9, 8.7, Ar), 7.87 (2H, d, J = 8.3, Ar), 7.99 (2H, dt, J = 1.9, 8.7, Ar); ^{13}C NMR (75.5 Mhz) δ 146.4, 144.6, 140.9, 139.6, 139.2, 130.4, 129.4, 128.9, 128.4, 128.3, 128.1, 127.7, 22.0; IR (film, cm^{-1}) ν 3019, 1594, 1319, 1309, 1292, 1215, 1155, 1109, 758; HRMS (EI$^+$) calcd for $C_{19}H_{16}O_2S$ [M^+]: m/z 308.0871; found: m/z 308.0870; Anal. calcd for $C_{19}H_{16}O_2S$: C 74.00, H 5.23, N 0.00; found: C 73.60, H 5.37, N 0.00%.

6.5 Preparation of α-Amino Acids *via* the Rhodium Catalysed Conjugate Addition of Boronic Acids: Racemic

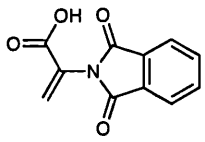
2-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-acrylic acid ethyl ester (Ethyl-α-phthalimidoacrylate) 163



Prepared in accordance with the literature procedure.[141]

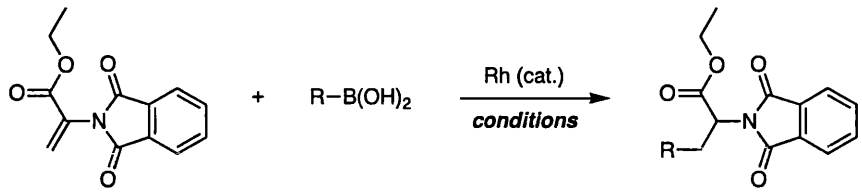
To a solution of phthalimide (7.36 g, 50.0 mmol), triphenylphosphine (1.31 g, 5.0 mmol), and sodium acetate (2.05 g, 25.0 mmol) in 100 mL of toluene at 105 °C were added sequentially acetic acid (1.5 g, 25.0 mmol) and ethylpropiolate (4.90 g, 50.0 mmol). After 18 h, the cooled reaction mixture was directly chromatographed on silica gel (petrol:ethyl acetate, 4:1) to yield 10.04 g (82% yield) of ethyl-α-phthalimidoacrylate **163**. R_f (petrol:ethyl acetate, 4:1) 0.34; mp 81-82 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (3H, t, J = 7.2, CH_3), 4.29 (2H, q, J = 7.2, CH_2), 5.99 (1H, s, $=CH_2$), 6.69 (1H, s, $=CH_2$), 7.78 (2H, dd, J = 3.0, 5.5, Ar), 7.93 (2H, dd, J = 3.0, 5.5, Ar); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 166.9, 162.6, 134.9, 132.2, 129.8 128.2, 124.3, 62.5, 14.5; IR (film, cm^{-1}) ν 2989, 1774, 1723, 1635, 1607, 1468, 1447, 1401, 1381, 1287, 1199, 1147, 1085, 1022, 952, 941, 885, 792, 754, 730, 711, 675, 644; HRMS (FAB$^+$) calcd for $C_{13}H_{12}NO_4$ [MH^+]: m/z 246.0766; found: m/z 246.0763; Anal. calcd for $C_{13}H_{11}NO_4$: C 63.67, H 4.52, N 5.71; found: C 63.8, H 4.52, N 5.79%. Data identical to those in the literature.[141]

2-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-acrylic acid 166



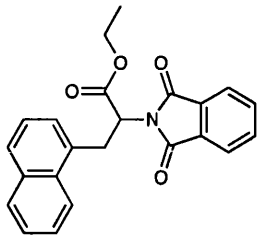
Ethyl-α-phthalimidoacrylate (500 mg, 2.04 mmol), in tetrahydrofuran (4 mL) was added to a solution of sodium hydroxide (408 mg, 10.2 mmol) in water (10 mL), and the mixture refluxed for 6 hours. After cooling to room temperature, the tetrahydrofuran portion was removed under reduced pressure, the resultant solution was acidified with 2 M hydrochoric acid and the product was extracted with ethyl acetate (4 × 20 mL). The extract was washed with brine, dried over $MgSO_4$, and evaportated to dryness under reduced pressure to afford the title compound as a colourless solid in 82% yield (369 mg). Mp 101-102 °C; ^{1}H NMR (400 MHz, MeOD-d^4) δ 6.00 (1H, s), 6.51 (1H, s), 7.51 (1H, d, J = 7.6), 7.57 (1H, dt, J = 7.6, 1.2), 7.65 (1H, dt, J = 7.6, 1.2), 7.99 (1H, d, J = 7.6); IR (Nujol, cm^{-1}) ν 4329, 4257, 2722, 1675, 1459, 1375, 1306, 1148, 895, 761, 724; ^{1}H NMR (300 MHz, DMSO-d_6) δ 168.1, 167.9, 165.3, 138.2, 134.1, 131.9, 131.0, 130.5, 129.4, 129.7, 127.9; ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 168.1, 167.9, 165.3, 138.15, 134.1, 131.9, 130.5, 129.9, 129.7, 127.9; HRMS (FAB$^-$) calcd for $C_{11}H_6NO_4$ [M – H]: m/z 216.0297; found: m/z 216.0291.

Typical procedure for the rhodium-catalysed 1,4-addition of boronic acids to ethyl-α-phthalimidoacrylate



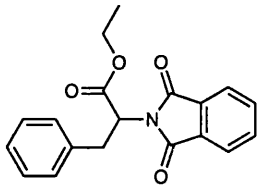
A suspension of ethyl-α-phthalimidoacrylate (1 equiv., 0.25 mmol), boronic acid (2 equiv., 0.5 mmol), and chloro-(1,5-cyclooctadiene)rhodium(I) dimer (5 mol%, 0.0125 mmol, 6 mg), in 3 mL of water was refluxed for 24 h under an air atmosphere. After this time ethyl acetate (10 mL) was added and the phases separated, the aqueous phase was further extracted with ethyl acetate (3 × 10 mL). The combined organics were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel (petrol:ethyl acetate) to afford the desired product.

2-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-3-naphthalen-1-yl-propionic acid ethyl ester 170a



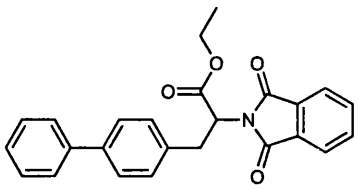
Ethyl-α-phthalimidoacrylate (61 mg, 0.25 mmol) and 1-naphthaleneboronic acid (86 mg, 0.5 mmol) were reacted under the standard protocol to give the desired product as a colourless solid (93 mg, 98% yield). R_f (petrol:ethyl acetate, 4:1) 0.38; mp 87-90 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.28 (3H, t, J = 7.2), 3.90 (1H, dd, J = 11.3, 14.7), 4.17 (1H, dd, J = 4.5, 14.7), 4.29 (2H, dq, J = 1.1, 7.2), 5.31 (1H, dd, J = 4.5, 11.3), 7.22-7.26 (2H, m), 7.43-7.51 (2H, m), 7.65-7.69 (3H, m), 7.72-7.76 (2H, m), 7.81 (1H, d, J = 8.7), 8.10 (1H, d, J = 8.7); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 167.7, 166.2, 132.8, 132.6, 131.7, 130.5, 130.3, 127.7, 126.6, 126.0, 125.2, 124.5, 124.0, 122.2, 121.8, 60.9, 51.6, 30.6, 12.9; IR (Nujol, cm^{-1}) ν 2924, 2852, 1773, 1744, 1711, 1597, 1462, 1386, 1276, 1251, 1199, 1103, 1028, 992, 945, 884, 798, 775, 720; HRMS (FAB$^+$) calcd for $C_{23}H_{20}NO_4$ [MH^+]: m/z 374.1392; found: m/z 374.1395; Anal. calcd for $C_{23}H_{19}NO_4$: C 73.98, H 5.13, N 3.75; found: C 73.6, H 5.12, N 3.75%. Data identical to those in the literature.[139]

2-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-3-phenyl-propionic acid ethyl ester 170b



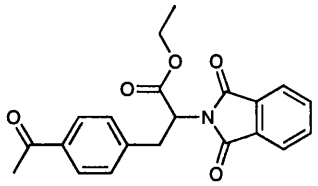
Ethyl-α-phthalimidoacrylate (61 mg, 0.25 mmol) and phenylboronic acid (61 mg, 0.5 mmol) were reacted under the standard protocol to give the desired product as a pale oil which solidified under vacuum (70 mg, 86% yield). R_f (petrol:ethyl acetate, 4:1) 0.42; mp 233-234 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (3H, t, J = 7.2, CH_3), 3.49-3.64 (2H, m, CH_2Ph), 4.25 (2H, dq, J = 1.9, 7.2, CH_2CH_3), 5.14 (1H, dd, J = 5.3, 10.9, NCH), 7.12-7.20 (5H, m, Ph), 7.66-7.70 (2H, m, Ar), 7.74-7.79 (2H, m, Ar); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 169.2, 167.9, 137.2, 134.5, 132.0, 129.2, 128.9, 127.2, 123.8, 62.4, 53.8, 35.0, 14.5; IR (Nujol, cm^{-1}) ν 3478, 3063, 3029, 2926, 2854, 1777, 1741, 1719, 1605, 1497, 1468, 1456, 1387, 1243, 1197, 1105, 1027, 952, 915, 875, 795, 751, 720, 698; HRMS (EI$^+$) calcd for $C_{19}H_{17}NO_4$ [M^+]: m/z 323.1158; found: m/z 323.1158. Data identical to those in the literature.[139]

3-Biphenyl-4-yl-2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-propionic acid ethyl ester 170c



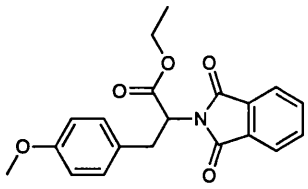
Ethyl-α-phthalimidoacrylate (61 mg, 0.25 mmol) and 4-biphenylboronic acid (99 mg, 0.5 mmol) were reacted under the standard protocol to give the desired product as a colourless solid (85 mg, 85% yield). R_f (petrol:ethyl acetate, 4:1) 0.44; mp 100-101 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.27 (3H, t, J = 7.2, CH_3), 3.55-3.69 (2H, m), 4.26 (2H, dq, J = 7.2, 1.5, CH_2CH_3), 5.19 (1H, dd, J = 6.0, 10.6, CH_2), 7.23-7.31 (3H, m), 7.35-7.44 (4H, m), 7.50 (2H, d, J = 7.9), 7.68 (2H, m), 7.79 (2H, m); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 169.2, 167.9, 141.0, 139.9, 136.3, 134.5, 132.0, 129.7, 129.1, 127.6, 127.3, 123.9, 62.5, 53.7, 34.7, 14.5; IR (film, cm^{-1}) ν 3028, 1777, 1743, 1718, 1613, 1521, 1488, 1468, 1445, 1389, 1271, 1243, 1197, 1118, 1099, 1027, 1009, 955, 884, 825, 756, 721, 699, 668; HRMS (FAB$^+$) calcd for $C_{25}H_{22}NO_4$ [MH^+]: m/z 400.1549; found: m/z 400.1540; [M^+]: calcd for $C_{25}H_{21}NO_4$ [M^+] m/z 399.1471; found m/z 399.1468.

3-(4-Acetyl-phenyl)-2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-propionic acid ethyl ester 170d



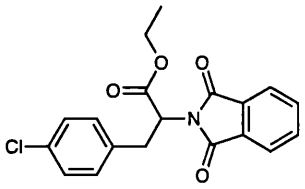
Ethyl-α-phthalimidoacrylate (61 mg, 0.25 mmol) and 4-acetylphenylboronic acid (82 mg, 0.5 mmol) were reacted under the standard protocol to give the desired product as a colourless gum (60mg, 66% yield). R_f (petrol:ethyl acetate, 4:1) 0.20; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (3H, t, J = 7.2, CH_3), 2.52 (3H, s, COH_3), 3.56-3.70 (2H, m, $CHCH_2$), 4.26 (2H, dq, J = 1.9, 7.2, CH_2CH_3), 5.17 (1H, dd, J = 6.0, 10.5, NCH), 7.28 (2H, d, J = 8.3, 2,6-Ar-C*H*), 7.68-7.74 (2H, m, Ar), 7.76-7.82 (4H, m, Ar, 3,5-Ar-C*H*); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 197.7, 168.5, 167.4, 142.5, 135.8, 134.2, 131.5, 129.1, 128.7, 123.6, 62.2, 52.9, 34.7, 26.6, 14.1; IR (Nujol, cm^{-1}) ν 2923, 2852, 1773, 1739, 1715, 1684, 1606, 1465, 1377, 1271, 1238, 1185, 1106, 1016, 954, 887, 714; HRMS (FAB^+) calcd for $C_{21}H_{20}NO_5$ [MH^+]: m/z 366.1341; found: m/z 366.1366; Anal. calcd for $C_{21}H_{19}NO_5$: C 69.03, H 5.24, N 3.38; found: C 68.9, H 5.28, N 3.83%.

2-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-3-(4-methoxy-phenyl)-propionic acid ethyl ester170e



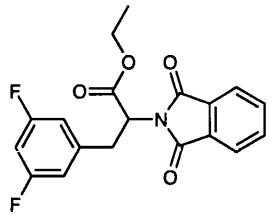
Ethyl-α-phthalimidoacrylate (61 mg, 0.25 mmol) and 4-methoxyphenylboronic acid (76 mg, 0.5 mmol) were reacted under the standard protocol to give the desired product as a colourless solid (78 mg, 88% yield). R_f (petrol:ethyl acetate, 4:1) 0.30; mp 100-104 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (3H, t, J = 7.2, CH_3), 3.43-3.58 (2H, m, CHCH_2), 3.70 (3H, s, OH_3), 4.25 (2H, dq, J = 1.9, 7.2, CH_2CH$_3$), 5.09 (1H, dd, J = 5.6, 10.7, NCH), 6.71 (2H, d, J = 8.7, 3,5-Ar-CH), 7.07 (2H, d, J = 8.7, 2,6-Ar-CH) 7.65-7.72 (2H, m, Ar), 7.75-7.81 (2H, m, Ar); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 168.9, 167.5, 158.3, 134.1, 131.6, 129.8, 128.8, 123.5, 113.9, 62.0, 55.1, 53.6, 33.8, 14.1; IR (Nujol, cm^{-1}) ν 2921, 2853, 1773, 1745, 1712, 1611, 1584, 1513, 1465, 1377, 1293, 1249, 1195, 1021, 726; HRMS (EI$^+$) calcd for $C_{20}H_{19}NO_5$ [M^+]: m/z 353.1263; found: m/z 353.1267; Anal. calcd for $C_{20}H_{19}NO_5$: C 67.98, H 5.42, N 3.96; found: C 67.9, H 5.44, N, 4.01%. Data identical to those in the literature.[139]

3-(4-Chloro-phenyl)-2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-propionic acid ethyl ester 170f



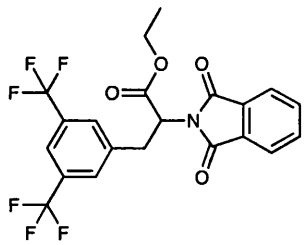
Ethyl-α-phthalimidoacrylate (61 mg, 0.25 mmol) and 4-chlorophenylboronic acid (78 mg, 0.5 mmol) were reacted under the standard protocol to give the desired product as a colourless gum (68 mg, 76% yield). R_f (petrol:ethyl acetate, 4:1) 0.47; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25, (3H, t, J = 7.2, CH_3), 3.47-3.61 (2H, m, $CHCH_2$), 4.25 (2H, dq, J = 1.7, 7.2, CH_2CH_3), 5.11 (1H, dd, J = 6.2, 10.4, CH), 7.10 (2H, d, J = 8.7, Ar), 7.16, (2H, d, J = 8.7, Ar), 7.69-7.72 (2H, m, Ar), 7.78-7.81 (2H, m, Ar); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 168.6, 167.5, 135.3, 134.2, 132.7, 131.5, 130.2, 128.7, 123.5, 62.1, 53.1, 34.0, 14.1; IR (Nujol, cm^{-1}) ν 3064, 2981, 2931, 2871, 2476, 1905, 1778, 1723, 1613, 1598, 1493, 1468, 1446, 1385, 1276, 1242, 1197, 1112, 1094, 1027, 955, 883, 811; HRMS (FAB$^+$) calcd for $C_{19}H_{17}ClNO_4$ [MH^+]: m/z 358.0846; found: m/z 358.0858; calcd for $C_{19}H_{17}{}^{37}ClNO_4$, m/z 360.0817; found: m/z 360.0833. Data identical to those in the literature.[139]

3-(3,5-Difluoro-phenyl)-2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-propionic acid ethyl ester 170g



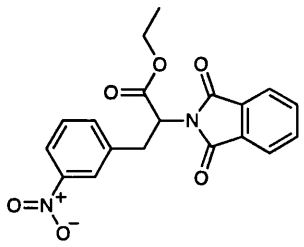
Ethyl-α-phthalimidoacrylate (61 mg, 0.25 mmol) and 3,5-difluorobenzeneboronic acid (79 mg, 0.5 mmol) were reacted under the standard protocol to give the desired product as a colourless solid (80 mg, 89% yield). R_f (petrol:ethyl acetate, 4:1) 0.47; mp 90-92 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (3H, t, J = 7.2, CH_3), 3.49-3.62 (2H, m, CH_2Ph), 4.25 (2H, dq, J = 7.2, 3.2, CH_2CH$_3$), 5.10 (1H, dd, J = 5.6, 11.2, CH), 6.59 (1H, tt, J = 2.4, 8.8, CH[CF]$_2$), 6.72 (2H, app d, J = 2.0, CHCCH$_2$), 7.72 (2H, app dd, J = 3.2, 5.6, phth), 7.82 (2H, app dd, J = 3.2, 5.6, phth); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 168.4, 167.5, 164.3(d, $J^{C\text{-}F}$ = 12.3), 161.8 (d, $J^{c\text{-}F}$ = 13.1), 140.9, 134.5, 131.6, 123.8, 112.0 (d, J = 24.5), 102.8 (t, J = 24.5), 62.6, 53.2, 34.9, 14.6; IR (Nujol, cm^{-1}) ν 2921, 2726, 2360, 1774, 1739, 1714, 1627, 1595, 1463, 1378, 1338, 1269, 1249, 1225, 1197, 1179, 1155, 1141, 1120, 1099, 1088, 1065, 1027, 987, 971, 949, 888, 875, 852, 789, 723; HRMS (FAB$^+$) calcd for $C_{19}H_{16}F_2NO_4$ [MH^+]: m/z 360.1047; found: m/z 360.1044; Anal. calcd for $C_{19}H_{15}F_2NO_4$: C 63.51, H 4.21, N 3.90; found: C 63.5, H 4.27, N 3.95%.

3-(3,5-Bis-trifluoromethyl-phenyl)-2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-propionic acid ethyl ester 170h



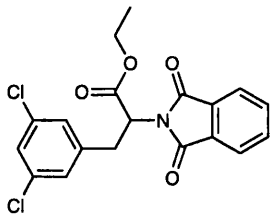
Ethyl-α-phthalimidoacrylate (61 mg, 0.25 mmol) and 3,5-bis(trifluoromethyl)benzene boronic acid (129 mg, 0.5 mmol) were reacted under the standard protocol to give the desired product as a colourless solid (103 mg, 90% yield). R_f (petrol:ethyl acetate, 4:1) 0.48; mp 70-71 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (3H, t, J = 7.2, CH_3), 3.60-3.77 (2H, m, CH_2Ph), 4.27 (2H, dq, J = 7.2, 2.8, CH_2CH_3), 5.14 (1H, dd, J = 5.6, 10.8, C*H*), 7.64 (2H, br s), 7.68 (1H, br s), 7.73 (2H, app dd, J = 3.2, 5.6, phth), 7.81 (2H, app dd, J = 3.2, 5.6, phth); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 168.1, 167.4, 139.7, 134.6, 131.9 (q, J = 33.0), 131.5, 129.4 (br d, J = 2.3), 124.6, 123.8, 121.8, 121.2 (pent, J = 3.8), 62.8, 53.0, 35.0, 14.5; IR (Nujol, cm^{-1}) ν 3484, 3065, 2984, 2932, 2856, 1780, 1721, 1624, 1469, 1448, 1378, 1278, 1244, 1177, 1139, 1099, 1028, 960, 925, 902, 880, 859, 842, 788, 761, 720, 708; HRMS (FAB$^+$) calcd for $C_{21}H_{16}F_6NO_4$ [MH^+]: m/z 460.0984; found: m/z 460.0980; Anal. calcd for $C_{21}H_{15}F_6NO_4$: C 54.91, H 3.29, N 3.05; found: C 54.8, H 3.33, N 3.08%.

2-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-3-(3-nitrophenyl)-propionic acid ethyl ester 170i



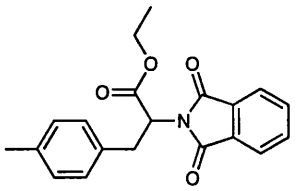
Ethyl-α-phthalimidoacrylate (61 mg, 0.25 mmol) and 3-nitrophenylboronic acid (84 mg, 0.5 mmol) were reacted under the standard protocol to give the desired product as a colourless solid (61mg, 66% yield). R_f (petrol:ethyl acetate, 4:1) 0.25; mp 99-102 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (3H, t, J = 7.2, CH_3), 3.59-3.76 (2H, m, CH_2CH), 4.26 (2H, dq, J = 1.9, 7.2, CH_2CH_3), 5.16 (1H, dd, J = 4.9, 10.5, NCH), 7.40 (1H, app t, J = 7.5, 5-Ar-C*H*), 7.54 (1H, d, J = 7.5, 6-Ar-C*H*), 7.70-7.75 (2H, m, Ar), 7.78-7.82 (2H, m, Ar), 8.03 (1H, d, J = 8.3, 4-Ar-C*H*), 8.06 (1H, s, 2-Ar-C*H*); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 168.2(CO_2), 167.4(CO), 148.3, 139.0, 135.1, 134.4, 131.4, 129.6, 123.9, 123.7, 122.1, 62.4(OCH_2), 52.9(*CH*), 34.5(CH_2), 14.1(CH_3); IR (Nujol, cm^{-1}) ν 2923, 2853, 1774, 1745, 1714, 1530, 1466, 1386, 1350, 1277, 1241, 1200, 1105, 1029, 951, 904, 874, 830, 813, 739, 721, 691; HRMS (FAB$^+$) calcd for $C_{19}H_{17}N_2O_6$ [MH^+]: m/z 369.1087; found: m/z 369.1099; Anal. calcd for $C_{19}H_{16}N_2O_6$: C 61.95, H 4.38, N 7.61; found: C 61.6, H 4.42, N 7.64%.

3-(3,5-Dichloro-phenyl)-2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-propionic acid ethyl ester 170j



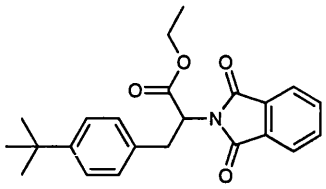
Ethyl-α-phthalimidoacrylate (61 mg, 0.25 mmol) and 3,5-dichlorobenzeneboronic acid (95 mg, 0.5 mmol) were reacted under the standard protocol to give the desired product as a colourless solid (91 mg, 93% yield). R_f (petrol:ethyl acetate, 4:1) 0.53; mp 74-76 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (3H, t, J = 7.2, CH_3), 3.44-3.60 (2H, m, CH_2Ph), 4.25 (2H, dq, J = 7.2, 3.2, CH_2CH$_3$), 5.09 (1H, dd, J = 5.2, 11.2, CH), 7.08 (2H, d, J = 2.0, CHCCH$_2$), 7.15 (1H, t, J = 2.0, CH[Ccl]$_2$), 7.73 (2H, app dd, J = 2.8, 5.6, phth), 7.83 (2H, app dd, J = 2.8, 5.6, phth); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 168.3, 167.6, 140.5, 135.1, 134.5, 131.6, 127.6, 127.4, 123.9, 62.7, 53.2, 34.7, 14.6; IR (Nujol, cm^{-1}) ν 2954, 2856, 1771, 1750, 1713, 1590, 1567, 1460, 1377, 1279, 1257, 1228, 1193, 1180, 1086, 1067, 1027, 953, 916, 890, 874, 850, 796, 721; HRMS (FAB$^+$) calcd for $C_{19}H_{16}{}^{35}Cl_2NO_4$ [M H^+]: m/z 392.0456; found: m/z 392.0458; Anal. calcd for $C_{19}H_{15}Cl_2NO_4$: C 58.18, H 3.85, N 3.57; found: C 57.8, H 3.92, N 3.62%.

2-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-3-*p*-tolyl-propionic acid ethyl ester 170k



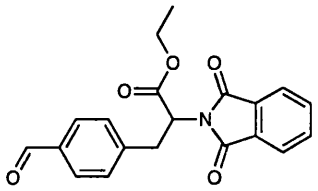
Ethyl-α-phthalimidoacrylate (61 mg, 0.25 mmol) and 4-methylphenylboronic acid (68 mg, 0.5 mmol) were reacted under the standard protocol to give the desired product as a colourless solid (65 mg, 77% yield). R_f (petrol:ethyl acetate, 4:1) 0.48; mp 73-75 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25 (3H, t, J = 7.2, CH_2CH_3), 2.22 (3H, s, $ArCH_3$), 3.45-3.55 (2H, m, $CHCH_2$), 4.24 (2H, m, CH_2CH_3), 5.12 (1H, dd, J = 5.8, 10.7, CH), 6.98 (2H, d, J = 8.1, Ar), 7.05 (2H, d, J = 8.1, Ar), 7.68 (2H, dd, J = 3.2, 5.5, Ar), 7.78 (2H, dd, J = 3.2, 5.5, Ar); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 169.3, 167.9, 135.7, 134.4, 134.1, 132.0, 129.6, 129.1, 123.8, 62.4, 53.9, 34.6, 21.4, 14.5; IR (film, cm^{-1}) ν 3024, 2982, 2925, 2871, 1777, 1740, 1715, 1615, 1516, 1468, 1446, 1388, 1243, 1197, 1115, 1099, 1026, 953, 881, 789, 755, 719, 668, 604; HRMS (FAB$^+$) calcd for $C_{20}H_{20}NO_4$ [MH^+]: m/z 338.1392; found: m/z 338.1389. Data identical to those in the literature.[139]

3-(4-*tert*-Butyl-phenyl)-2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-propionic acid ethyl ester 170l



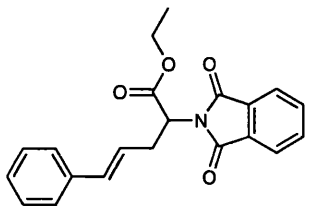
Ethyl-α-phthalimidoacrylate (61 mg, 0.25 mmol) and 4-*tert*-butylbenzeneboronic acid (89 mg, 0.5 mmol) were reacted under the standard protocol to give the desired product as a colourless solid (69 mg, 73% yield). R_f (petrol:ethyl acetate, 4:1) 0.47; mp 107-109 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (9H, s, $(CH_3)_3$), 1.25 (3H, t, J = 6.8, CH_3), 3.48-3.60 (2H, m, CH_2Ph), 4.24 (2H, dq, J = 6.8, 3.6, CH_2CH$_3$), 5.15 (1H, dd, J = 6.0, 11.2, C*H*), 7.10 (2H, app d, J = 8.8), 7.20 (2H, app d, J = 8.8), 7.67 (2H, app dd, J = 3.2, 5.6, phth), 7.78 (2H, app dd, J = 3.2, 5.6, phth); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 169.1, 167.7, 149.7, 134.2, 133.9, 131.9, 128.7, 125.6, 123.6, 62.4, 53.8, 34.8, 34.5, 31.7, 14.6; IR (Nujol, cm^{-1}) ν 2923, 2853, 1777, 1748, 1719, 1612, 1514, 1466, 1387, 1320, 1279, 1245, 1196, 1128, 1103, 1026, 994, 951, 886, 824, 771, 721; HRMS (FAB$^+$) calcd for $C_{23}H_{26}NO_4$ [MH^+]: m/z 380.1862; found: m/z 380.1860. Data identical to those in the literature.[139]

2-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-3-(4-formyl-phenyl)-propionic acid ethyl ester 170m



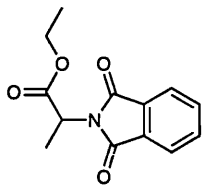
Ethyl-α-phthalimidoacrylate (61 mg, 0.25 mmol) and 4-formylphenylboronic acid (75 mg, 0.5 mmol) were reacted under the standard protocol to give the desired product as a colourless solid (52 mg, 59% yield). R_f (petrol:ethyl acetate, 4:1) 0.22; mp softens at 86 °C melts at 111-115 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (3H, t, J = 7.2, CH_3), 3.59-3.73 (2H, m, $CHCH_2$), 4.26 (2H, dq, J = 1.7, 7.2, CH_2CH_3), 5.18 (1H, dd, J = 6.0, 10.5, CH), 7.36 (2H, d, J = 7.9, Ar), 7.69-7.74 (4H, m, Ar), 7.78-7.80 (2H, m, Ar), 9.90 (1H, s, CHO); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 192.3, 168.8, 167.8, 144.5, 135.5, 134.7, 131.8, 130.5, 130.4, 130.0, 128.9, 124.0, 62.7, 53.2, 35.3, 14.5; IR (Nujol, cm^{-1}) ν 2925, 2853, 1769, 1743, 1713, 1697, 1607, 1577, 1466, 1386, 1308, 1283, 1240, 1216, 1195, 1172, 1098, 1087, 1026, 987, 947, 886, 875, 745, 719; HRMS (FAB$^+$) calcd for $C_{20}H_{18}NO_5$ [MH^+]: m/z 352.1185; found: m/z 352.1196.

2-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-5-phenyl-pent-4-enoic acid ethyl ester 170n



Ethyl-α-phthalimidoacrylate (61 mg, 0.25 mmol) and *trans*-2-phenylvinylboronic acid (74 mg, 0.5 mmol) were reacted under the standard protocol to give the desired product as a pale gum (84mg, 96% yield). R_f (petrol:ethyl acetate, 4:1) 0.44; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25 (3H, t, J = 7.2, CH_3), 3.16 (2H, app t, J = 7.9, CH_2CH), 4.24 (2H, q, J = 7.2, CH_2CH_3), 5.01 (1H, t, J = 7.9, NCH), 6.11 (1H, dt, J = 7.9, 15.8, $=CHCH_2$), 6.42 (1H, d, J = 15.8, PhCH=CH), 7.14-7.24 (5H, m, Ph), 7.68-7.72 (2H, m, Ar), 7.81-7.85 (2H, m, Ar); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 169.1, 168.0, 137.3, 134.5, 133.9, 132.1, 128.8, 127.7, 126.6, 125.3, 123.9, 62.4, 52.4, 33.1, 14.5; IR (Nujol, cm^{-1}) ν 3641, 3478, 3059, 3026, 2926, 2853, 1776, 1743, 1720, 1612, 1598, 1496, 1468, 1449, 1388, 1289, 1243, 1195, 1116, 1088, 1027, 968, 856, 745, 720; HRMS (FAB^+) calcd for $C_{21}H_{20}NO_4$ [MH^+]: m/z 350.1392; found: m/z 350.1398.

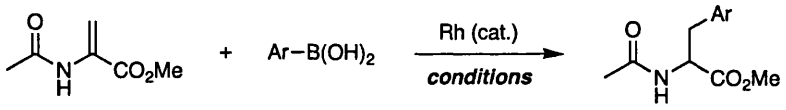
2-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-propionic acid ethyl ester 173



A suspension of ethyl-α-phthalimidoacrylate (1 equiv., 0.25 mmol), butylboronic acid (51 mg, 0.5 mmol), and chloro-(1,5-cyclooctadiene)rhodium(I) dimer (6.0 mg, 0.0125 mmol), in 3 mL of water was refluxed for 24 h under an air atmosphere in a sealed pressure tube. After this time ethyl acetate (10 mL) was added and the phases separated, the aqueous phase was further extracted with ethyl acetate (3 × 10 mL). The combined organics were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel (petrol:ethyl acetate, 4:1) to give the title compound in 63% yield (39 mg). R_f (petrol:ethyl acetate, 4:1) 0.41; mp 60-62 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24 (3H, t, J = 7.2, CH_2CH_3), 1.70 (3H, d, J = 7.2, $CHCH_3$), 4.21 (2H, dq, J = 1.3, 7.2, CH_2), 4.97 (1H, q, J = 7.2, CH), 7.74 (2H, dd, J = 3.0, 5.3, Ar), 7.87 (2H, dd, J = 3.0, 5.3, Ar); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 170.1, 167.8, 134.5, 132.3, 123.9, 62.2, 48.0, 15.7, 14.5; IR (Nujol, cm^{-1}) ν 2922, 2853, 1783, 1716, 1611, 1464, 1385, 1303, 1262, 1233, 1201, 1152, 1099, 1082, 1064, 1021, 1008, 934, 883, 799, 761, 719; HRMS (FAB^+) calcd for $C_{13}H_{14}NO_4$ [MH^+]: m/z 248.0923; found: m/z 248.0920;

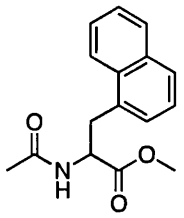
6.6 Preparation of α-Amino Acids *via* the Rhodium Catalysed Conjugate Addition of Boronic Acids: Enantioselective

Typical procedure for the rhodium-catalysed 1,4-addition of boronic acids to methyl-2-acetamidoacrylate



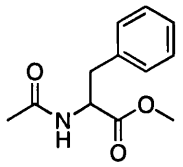
A Shlenk tube purged with nitrogen was charged with $[Rh(acac)(C_2H_4)_2]$ (3.9 mg, 15 μmol), ligand ***(R,R,R)*-179** (15.1 mg, 16 μmol), methyl-2-acetamidoacrylate (72 mg, 0.5 mmol), boronic acid (2 mmol), sodium fluoride (63 mg, 1.5 mmol) and dioxane (1.5 mL). The mixture was stirred at room temperature for 30 minutes and water (150 μL) added. The mixture was then stirred under an atmosphere of nitrogen at 100 °C for 24 hours. After cooling to room temperature the solution was dissolved in ethyl acetate (3 mL) and water (5 mL) was added. The aqueous layer was separated and extracted with ethyl acetate (3 × 5 mL), the combined organics were washed with brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by silica column chromatography (petrol:ethyl acetate) to yield the title compound in as a colourless solid.

N-acetyl-3-(1-naphthyl)alanine methyl ester 75a



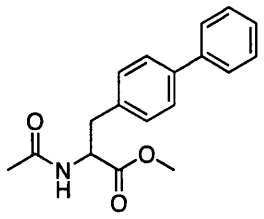
Methyl-2-acetamidoacrylate (71.5 mg, 0.5 mmol) and 1-naphthaleneboronic acid (344 mg, 2 mmol), were reacted under the standard protocol to generate the desired compound as a colourless solid (125 mg, 92% yield). R_f (petrol:ethyl acetate, 1:1) 0.20; mp 90-91 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.91 (3H, s), 3.48 (1H, dd, J = 6.6, 14.1), 3.59 (1H, dd, J = 6.3, 14.1), 3.61 (3H, s), 5.01 (1H, m), 6.29 (1H, br d, J = 7.9), 7.22 (1H, app. d, J = 6.8), 7.36 (1H, app. t, J = 8.3), 7.45-7.56 (2H, m), 7.74 (1H, d, J = 8.3), 7.83 (1H, d, J = 7.9), 8.07 (1H, d, J = 8.3); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 172.5, 170.0, 134.0, 132.6, 132.4, 129.0, 128.1, 127.5, 126.5, 126.0, 125.4, 123.7, 53.6, 52.6, 35.4, 23.4; IR (film, cm^{-1}) ν 3065, 3010, 2952, 1744, 1657, 1598, 1546, 1512, 1437, 1374, 1276, 1216, 1178, 1129, 1018, 982, 755, 666; Optical rotation: $[\alpha]_D^{25}$ –13.5° (c=0.445, EtOH), lit: (*S*) $[\alpha]_D^{25}$ –18.8° (c=1.0, EtOH)[196]; HRMS (FAB$^+$) calcd for $C_{16}H_{18}NO_3$ [MH^+]: m/z 272.1287; found: m/z 272.1275 (100%); Calcd for $C_{15}{}^{13}CH_{18}NO_3$ [MH^+] m/z 273.1320; found: m/z 273.1324 (18.1%); Anal. calcd for $C_{16}H_{17}NO_3$: C 70.83, H 6.32, N 5.16; found: C 71.2, H 6.34, N 5.04%. Data identical to those in the literature.[196]

N-Acetylphenylalanine methyl ester 75b



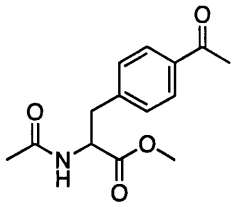
Methyl-2-acetamidoacrylate (71.5 mg, 0.5 mmol) and phenylboronic acid (244 mg, 2 mmol), were reacted under the standard protocol to generate the desired compound as a colourless solid (85 mg, 77% yield). R_f (petrol:ethyl acetate, 1:1) 0.22; mp 66-68 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.98 (3H, s), 3.09 (1H, dd, J = 5.7, 13.8), 3.16 (1H, dd, J = 6.0, 13.8), 3.72 (3H, s), 4.88 (1H, m), 5.95 (1H, br d, J = 6.4), 7.07-7.10 (2H, m), 7.21-7.32 (3H, m); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 172.5, 170.0, 136.2, 129.6, 129.0, 127.5, 53.5, 52.7, 38.2, 23.5; IR (film, cm^{-1}) ν 3287, 3064, 3029, 2953, 2848, 1743, 1657, 1544, 1437, 1374, 1274, 1218, 1178, 1129, 1080, 1031, 1012, 985, 756, 701; MS (FAB$^+$): m/z 222.1 (100%, MH$^+$); Optical rotation: $[\alpha]_D^{25}$ +5.63° (c=0.355, EtOH), lit: (*R*) $[\alpha]_D^{20}$ –12.7° (c=5.00, EtOH)[197]; HRMS (FAB$^+$) calcd for $C_{12}H_{16}NO_3$ [MH^+]: m/z 222.1130; found: m/z 222.1124; Anal. calcd for $C_{12}H_{15}NO_3$: C 65.14, H 6.83, N 6.33; found: C 65.0, H 6.93, N 6.15%. Data identical to those in the literature.[198]

N-Acetyl-3-(4-biphenyl)alanine methyl ester 75c



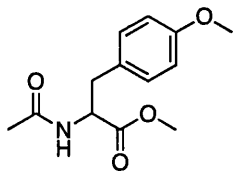
Methyl-2-acetamidoacrylate (71.5 mg, 0.5 mmol) and 4-biphenylboronic acid (396 mg, 2 mmol), were reacted under the standard protocol to generate the desired compound as a colourless solid (117 mg, 79% yield). R_f (petrol:ethyl acetate, 1:1) 0.18; mp 152-154 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.98 (3H, s), 3.11 (1H, dd, J = 6.0, 13.9), 3.19 (1H, dd, J = 5.7, 13.9), 3.72 (3H, s), 4.91 (1H, m), 6.25 (1H, br d, J = 7.5), 7.16 (2H, d, J = 8.1), 7.32 (1H, t, J = 7.5), 7.42 (2H, app t, J = 7.5), 7.51 (2H, d, J = 8.1), 7.56 (2H, d, J = 7.5); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 172.2, 169.9, 140.7, 140.1, 135.1, 129.8, 129.0, 127.5, 127.4, 127.1, 53.5, 52.7, 37.8, 23.5; IR (film, cm^{-1}) ν 3348, 3029, 2954, 2358, 1752, 1653, 1533, 1488, 1437, 1375, 1217, 1172, 1129, 1007, 830, 761, 728, 695, 668; MS (FAB$^+$): m/z 298.1 (100%, MH$^+$); Optical rotation: $[\alpha]_D^{25}$ +11.1° (c=0.09, EtOH); HRMS (FAB$^+$) calcd for $C_{18}H_{20}NO_3$ [MH^+]: m/z 298.1443; found: m/z 298.1430; Anal. calcd for $C_{18}H_{19}NO_3$: C 72.71, H 6.44, N 4.71; found: C 72.6, H 6.39, N 4.66%.

N-Acetyl-3-(4-acetylphenyl)alanine methyl ester 75d



Methyl-2-acetamidoacrylate (71.5 mg, 0.5 mmol) and 4-acetylphenylboronic acid (328 mg, 2 mmol), were reacted under the standard protocol to generate the desired compound as a colourless solid (48 mg, 36% yield). R_f (petrol:ethyl acetate, 1:2) 0.17; mp 125 softens 144-146 melts °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.96 (3H, s), 2.55 (3H, s), 3.09 (1H, dd, J = 6.0, 14.1), 3.20 (1H, dd, J = 6.0, 14.1), 3.70, (3H, s), 4.88 (1H, dt, J = 6.0, 7.8), 6.18 (1H, br d, J = 7.5), 7.18 (2H, d, J = 8.3), 7.85 (2H, d, J = 8.3); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 197.8, 171.9, 169.8, 141.8, 136.1, 129.7, 128.8, 53.3, 52.9, 38.3, 27.0, 23.5; IR (film, cm^{-1}) ν 3286, 3076, 3016, 2959, 1746, 1678, 1608, 1549, 1216, 1183, 1126, 1017, 959, 832, 755, 666; Optical rotation: $[\alpha]_D^{25}$ +8.0° (c=0.125, EtOH); MS (FAB$^+$): m/z 264.1 (100%, MH$^+$); HRMS (FAB$^+$) calcd for $C_{14}H_{18}NO_4$ [MH^+]: m/z 264.1236; found: m/z 264.1220; Anal. calcd for $C_{14}H_{17}NO_4$: C 63.87, H 6.51, N 5.32; found: C 63.5, H 6.48, N 5.08%.

N-acetyl-3-(4-methoxyphenyl)alanine methyl ester 75e



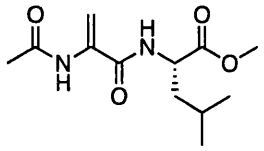
Methyl-2-acetamidoacrylate (71.5 mg, 0.5 mmol) and 4-methoxyphenylboronic acid (304 mg, 2 mmol), were reacted under the standard protocol to generate the desired compound as a colourless solid (92 mg, 73% yield). R_f (petrol:ethyl acetate, 1:1) 0.18; mp 94 °C (lit. 104-106 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.97 (3H, s), 3.00 (1H, dd, J = 5.8, 13.8), 3.07 (1H, dd, J = 5.9, 13.8), 3.71 (3H, s), 3.77 (3H, s), 4.82 (1H, m), 6.26 (1H, br d, J = 7.8), 6.82 (2H, d, J = 8.7), 7.01 (2H, d, J = 8.7); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 172.3, 169.8, 158.7, 130.3, 127.9, 114.1, 55.5, 53.6, 52.6, 37.3, 23.5; IR (film, cm^{-1}) ν 3431, 3019, 2955, 1743, 1675, 1612, 1513, 1438, 1374, 1250, 1216, 1178, 1128, 1035, 754, 669; Optical rotation: $[\alpha]_D^{25}$ +13.3° (c=0.075, EtOH), lit: (*S*) $[\alpha]_D^{25}$ +23.3° (c=1.0, EtOH)[198]; MS (FAB$^+$): m/z 252.1 (100%, MH^+); HRMS (FAB$^+$) calcd for $C_{13}H_{18}NO_4$ [MH^+]: m/z 252.1236; found: m/z 252.1223; Anal. calcd for $C_{13}H_{17}NO_4$: C 62.14, H 6.82, N 5.57; found: C 62.2, H 6.76, N 5.37. Data identical to those in the literature.[198]

Chiral HPLC Data

Chiral HPLC. The enantiomeric excess was determined by HPLC using either Daicel Chiralcel OD or Chiralpak AD Columns (4.6 x 250 mm) at ambient temperature. The separation of mixtures under HPLC conditions is as follows: ***N*-acetylphenylalanine methyl ester 75b** (AD, 1.0 mL/min, 10% 2-PrOH:hexane), (*R*) t_{R1} = 10.2 min, (*S*) t_{R2} = 12.9 min; ***N*-acetyl-3-(1-naphthyl)alanine methyl ester 75a** (AD, 1.0 mL/min, 10% 2-PrOH:hexane), (*R*) t_{R1} = 11.2 min, (*S*) t_{R2} = 14.1 min; ***N*-acetyl-3-(4-biphenyl)alanine methyl ester 75c** (AD, 1.0 mL/min, 10% 2-PrOH:hexane), (*R*) t_{R1} = 13.5 min, (*S*) t_{R2} = 21.5 min; ***N*-acetyl-3-(4-acetylphenyl)alanine methyl ester 75d** (OD, 1.0 mL/min, 10% 2-PrOH:hexane), (*R*) t_{R1} = 32.2 min, (*S*) t_{R2} = 41.1 min; ***N*-acetyl-3-(4-methoxyphenyl)alanine methyl ester 75e** (AD, 1.0 mL/min, 10% 2-PrOH:hexane), (*R*) t_{R1} = 13.9 min, (*S*) t_{R2} = 17.8 min; ***N*-phthalimido-3-(1-naphthyl)alanine ethyl ester 170a** (AD, 1.0 mL/min, 10% 2-PrOH:hexane), (*S*) t_{R1} = 13.7 min, (*R*) t_{R2} = 15.4 min. Configurations were established for *N*-acetylphenylalanine methyl ester and *N*-acetyl-3-(1-naphthyl)alanine methyl ester by chiral HPLC (Chiralcel OJ) and comparison to the literature values.[199] Other analogous products which gave the same sign of optical rotation and which eluted in the same order by chiral HPLC (Chiralpak AD) were assigned the same absolute configuration. For example, **(R,R,R)-179** produced *N*-acetylphenylalanine and substituted *N*-acylphenylalanine derivatives which were eluted second by chiral HPLC (Chiralpak AD). All such products were assigned *S* absolute configuration. Configuration of *N*-phthalimido-3-(1-naphthyl)alanine ethyl ester was assigned by comparison of the HPLC (Chiralpak AD) elution times with those for a sample of *N*-phthalimidophenylalanine ethyl ester produced from L-phenylalanine ethyl ester.[200]

6.7 Rhodium-Catalysed Conjugate Additions of Boronic Acids to Dipeptides

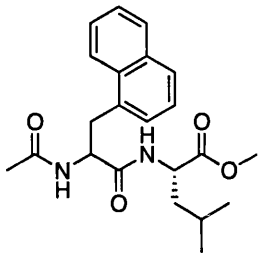
N-Acetyl-Δ-alanine-L-leucine methyl ester 187



Prepared in accordance to the literature procedure.[160]

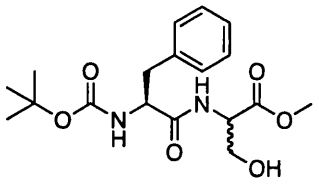
N,N-di-cyclohexylcarbodiimide (DCC) (2.06 g, 10 mmol) was added to a solution of 2-acetamidoacrylic acid (1.29 g, 10 mmol), L-leucine methyl ester hydrochloride (1.81 g, 10 mmol) and triethylamine (1.39 mL, 10 mmol) in 50 mL of ethyl acetate:chlorofom (1:1) at –5 °C. The reaction solution was stirred for 1 hour at –5 °C and then overnight at room temperature. The precipitated dicyclohexylurea was removed by filtration. The filtrate was washed successively with hydrochloric acid (0.1 M), potassium bicarbonate (0.1 M), and water. After drying over Na_2SO_4 the solvent was removed *in vacuo*. Purification by flash chromatography (petrol:ethyl acetate, 1:1) afforded the title compound as a colourless solid (324 mg, 13%). R_f (petrol:ethyl acetate, 1:1) 0.29; mp 94-98 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.96 (6H, d, J = 4.8), 1.59-1.72 (3H, m), 2.11 (3H, s), 3.76 (3H, s), 4.63-4.69 (1H, m), 5.28 (1H, s), 6.48 (1H, s), 6.58 (1H, br d, J = 5.7), 8.00 (1H, br s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 172.3, 168.3, 163.0, 132.8, 100.9, 51.5, 50.3, 40.2, 23.9, 23.7, 21.8, 20.8; IR (film, cm^{-1}) ν 2959, 2103, 1739, 1649, 1627, 1505, 1436, 1370, 1204, 1152, 1026, 976, 890, 754; MS (FAB$^+$): *m/z* 257.1 (100%, MH$^+$); HRMS (FAB$^+$) calcd for $C_{12}H_{21}N_2O_4$ [*MH*$^+$]: *m/z* 257.1501; found: *m/z* 257.1490.

N-Acetyl-3-(1-naphthyl)alanine-L-leucine methyl ester 188



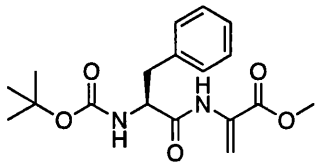
A Shlenk tube purged with nitrogen was charged with $[Rh(acac)(C_2H_4)_2]$ (3.9 mg, 15 μmol), ligand **(*rac*)-BINAP** (10.3 mg, 16 μmol), *N*-acetyl-Δ-alanine-L-leucine methyl ester (128 mg, 0.5 mmol), 1-naphthaleneboronic acid (344 mg, 2 mmol), NaF (63 mg, 1.5 mmol) and dioxane (1.5 mL). The mixture was stirred at room temperature for 30 minutes and water (150 μL) added. The mixture was then stirred under an atmosphere of nitrogen at 100 °C for 24 hours. After cooling to room temperature the solution was dissolved in ethyl acetate (3 mL) and water (5 mL) was added. The aqueous layer was separated and extracted with ethyl acetate (3 × 5 mL), the combined organics were washed with brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by silica column chromatography (petrol:ethyl acetate, 1:1) to yield the title compound in as a colourless solid (30 mg, 16%). mp softens 138°C melts 148-150 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.83 (3H, d, *J* = 6.0), 0.84 (3H, d, *J* = 6.0), 1.33-1.51 (3H, m), 1.96 (3H, s), 3.40 (1H, dd, *J* = 8.1, 13.8), 3.59 (1H, dd, *J* = 8.1, 13.8), 3.60 (3H, s), 4.39-4.46 (1H, m), 4.84 (1H, dt, *J* = 6.0, 8.1), 6.06 (1H, d, *J* = 7.8), 6.57 (1H, d, *J* = 7.8), 7.33-7.39 (2H, m), 7.46-7.57 (2H, m), 7.73-7.77 (1H, m), 7.85 (1H, dd, *J* = 1.5, 8.1), 8.24 (1H, d, *J* = 8.4); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 172.6, 171.0, 170.4, 134.3, 132.9, 132.4, 129.2, 128.4, 128.4, 127.0, 126.3, 125.7 124.2, 54.6, 52.6, 51.3, 42.0, 36.3, 25.0, 23.6, 23.0, 22.4; IR (film, cm^{-1}) *ν* 3019, 2958, 2872, 2361, 1742, 1651, 1548, 1437, 1387, 1371, 1216, 1153, 1018, 754, 668; MS (FAB^+): *m/z* 385.2 (100%, MH^+); HRMS (FAB^+) calcd for $C_{22}H_{29}N_2O_4$ [MH^+]: *m/z* 385.2127; found: *m/z* 385.2114; Anal. calcd for $C_{22}H_{28}N_2O_4$: C 68.73, H 7.34, N 7.29; found: C 68.4, H 7.31, N 6.95%.

N-(*tert*-butoxycarbonyl)-L-phenylalanine-D,L-serine methyl ester 191



To a stirred and cooled (–10 °C) solution of *N*-(*tert*-butoxycarbonyl)-phenyl alanine (1.0 g, 3.9 mmol), D,L-serine methyl ester hydrochloride salt (607 mg, 3.9 mmol), triethylamine (544 μL, 3.9 mmol) and HOBt·H_2O (580 mg, 4.3 mmol) in 1,2-dimethoxyethane (6.0 mL) a solution of DCC (885 mg, 4.3 mmol) in 1,2-dimethoxyethane (4.0 mL) was added. Stirring was continued at room temperature for 24 hours. Dicyclohexylurea was filtered off and washed with a small volume of ethyl acetate. The filtrate was diluted with ethyl acetate, extracted with sat. $NaHCO_3$ (*aq.*) (3 × 4 mL), 2M HCl (5 × 4 mL), sat. $NaHCO_3$ (*aq.*) (4 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Further purification, was performed by flash silica chromatography (petrol-ethyl acetate 1:1) to afford the title compound as a colourless solid (710mg, 49% yield). R_f (petrol:ethyl acetate, 1:4) 0.46; R_f (petrol:ethyl acetate, 1:1) 0.18; ^{1}H NMR (300 MHz, $CDCl_3$+D_2O) mixture of two diastereoisomers δ 1.35 (4.5H, s), 1.36 (4.5H, s), 2.91-3.02 (1H, m), 3.11-3.19 (1H, m), 3.72 (3H, s), 3.70-3.75 (0.5H, m), 3.82-3.96 (1.5H, m), 4.50 (1H, m), 4.58 (0.5H, m), 4.65 (0.5H, m), 5.53 (0.25H, d, J = 7.5), 5.60 (0.25H, d, J = 8.4), 7.19-7.30 (5H, m), 7.37 (0.25H, d, J = 8.1), 7.55 (0.25H, d, J = 8.1); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 172.0, 171.9, 170.6, 170.6, 155.6, 136.4, 129.2, 129.1, 128.3, 128.2, 126.7, 126.6, 80.2, 80.0, 62.2, 62.0, 55.46 (br), 54.5, 54.4, 52.5, 52.4, 38.3, 28.0; MS (FAB$^+$); *m/z* 367.0 (67%, MH$^+$).

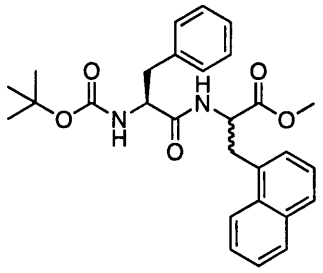
N-(*tert*-butoxycarbonyl)-L-phenylalanine-Δ-alanine methyl ester 192



Prepared in accordance to the published procedure.[165]

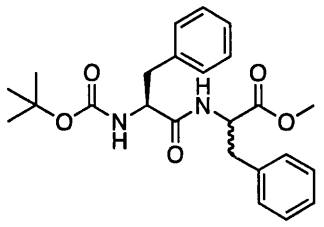
To an oven dried flask was added *N*-(*tert*-butoxycarbonyl)-L-phenylalanine-D,L-serine methyl ester (0.50 g, 1.36 mmol) in distilled dichloromethane (10 mL), copper(I) chloride (40 mg, 0.41 mmol, 30 mol%) and EDCI (288 mg, 1.5 mmol, 1.1 equiv.), the flask was sealed and the solution stirred under an atmosphere of nitrogen for 18 hrs at ambient temperature. The solution was diluted with dichloromethane (5 mL) and extracted with two portions of water (10 mL), dried over $MgSO_4$, filtered and evaporated to yield the desired product as a gummy foam in 70 % yield (333 mg). ^1H NMR (300 MHz, $CDCl_3$) δ 1.41 (9H, s), 3.12 (2H, br m), 3.79 (3H, s), 4.45 (1H, br m), 4.98 (1H, br s), 5.90 (1H, s), 6.62 (1H, s), 7.18-7.21 (1H, m), 7.24-7.34 (4H, m), 8.16 (1H, br s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 170.7, 164.4, 155.8, 136.7, 131.0, 129.6, 129.2, 127.5, 109.8, 80.9, 56.9, 53.3, 38.6, 28.6; MS (FAB^+): *m/z* 349.0 (45%, MH^+).

N-(*tert*-butoxycarbonyl)-L-phenylalanine-3-(1-naphthyl)alanine methyl ester 193a



A Shlenk tube purged with nitrogen was charged with $[Rh(acac)(C_2H_4)_2]$ (3.9 mg, 15 μmol), ligand (*rac*)-**BINAP** (10.3 mg, 16 μmol), *N*-(*tert*-butoxycarbonyl)-L-phenylalanine-Δ-alanine methyl ester (87 mg, 0.25 mmol), 1-naphthaleneboronic acid (172 mg, 1 mmol), sodium fluoride (32 mg, 0.75 mmol) and dioxane (1.5 mL). The mixture was stirred at room temperature for 30 minutes and water (150 μL) added. The mixture was then stirred at 100 °C under an atmosphere of nitrogen for 24 hours. After cooling to room temperature the solution was dissolved in ethyl acetate (3 mL) and water (5 mL) was added. The aqueous layer was separated and extracted with ethyl acetate (3 × 5 mL), the combined organics were washed with brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by silica column chromatography (petrol:ethyl acetate, 4:1) to yield the title compound as a colourless solid (70 mg, 59%). R_f (petrol:ethyl acetate, 4:1) 0.39; ^{1}H NMR (300 MHz, $CDCl_3$) mixture of two diastereoisomers δ 1.37 (9H, s), 2.88-3.05 (2H, m), 3.34 (0.5H, dd, J = 7.4, 14.3), 3.42-3.79 (1.5H, m), 3.52 (1.5H, s), 3.55 (1.5H, s), 4.30-4.35 (1H, m), 4.87-4.94 (1.5H, m), 5.03 (0.5H, d, J = 6.9), 6.39 (0.5H, d, J = 7.5), 6.55 (0.5H, d, J = 7.2). 7.06-7.36 (6H, m), 7.28-7.36 (1H, m), 7.45-7.57 (2H, m), 7.72-7.76 (1H, m), 7.82-7.86 (1H, m), 8.02-8.08 (1H, m); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 172.4, 172.1, 171.4, 171.3, 155.7, 136.9, 134.3, 134.3, 132.5, 132.5, 132.4, 129.8, 129.7, 129.3, 129.0, 129.0, 128.4, 127.9, 127.4, 126.8, 126.2, 125.7, 123.9, 80.5, 53.7, 53.5, 52.6, 38.8, 35.8, 28.6; MS (FAB$^+$): *m/z* 477.1 (76%, MH$^+$); HRMS (FAB$^+$) calcd for $C_{28}H_{33}N_2O_5$ [*MH*$^+$]: *m/z* 477.2389; found: *m/z* 477.2384.

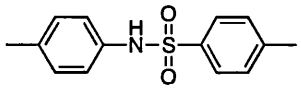
N-(*tert*-butoxycarbonyl)-L-phenylalanine-phenylalanine methyl ester 193b



A Schlenk tube purged with nitrogen was charged with [Rh(acac)(C_2H_4)$_2$] (3.9 mg, 15 μmol), ligand (*rac*)-**BINAP** (10.3 mg, 16 μmol), *N*-(*tert*-butoxycarbonyl)-L-phenylalanine-Δ-alanine methyl ester (87 mg, 0.25 mmol), phenylboronic acid (122 mg, 1 mmol), sodium fluoride (32 mg, 0.75 mmol) and dioxane (1.5 mL). The mixture was stirred at room temperature for 30 minutes and water (150 μL) added. The mixture was then stirred at 100 °C under an atmosphere of nitrogen for 24 hours. After cooling to room temperature the solution was dissolved in ethyl acetate (3 mL) and water (5 mL) was added. The aqueous layer was separated and extracted with ethyl acetate (3 × 5 mL), the combined organics were washed with brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by silica column chromatography (petrol:ethyl acetate, 4:1) to yield the title compound as a colourless solid (68 mg, 63%). R_f (petrol:ethyl acetate, 4:1) 0.17; ^{1}H NMR (300 MHz, $CDCl_3$) mixture of two diastereoisomers δ 1.38 (4.5H, s), 1.39 (4.5H, s), 2.90-3.11 (4H, m), 3.66 (3H, s), 4.36 (1H, m), 4.75-4.86 (1H, m), 4.99 (1H, m), 6.36 (0.5H, d, J = 7.2), 6.45 (0.5H, d, J = 7.5), 6.92-6.95 (1H, m), 6.97-7.00 (1H, m), 7.14-7.31 (8H, m); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 172.0, 171.8, 171.3, 171.2, 155.7, 137.0, 136.9, 136.0, 136.0, 129.8, 129.8, 129.6, 129.6, 129.1, 129.0, 128.9, 127.6, 127.5, 127.4, 80.6, 53.7, 53.4, 52.7, 38.7, 38.4, 38.3, 28.6; MS (FAB$^+$): *m/z* 427.1 (99%, MH$^+$); HRMS (FAB$^+$) calcd for $C_{24}H_{31}N_2O_5$ [*MH*$^+$]: *m/z* 427.2233; found: *m/z* 427.2224.

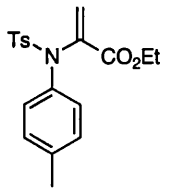
6.8 Synthesis of N-Aryl-α-Amino Acids: Rhodium Catalysis

4-Methyl-*N*-*p*-tolyl-benzenesulphonamide 195



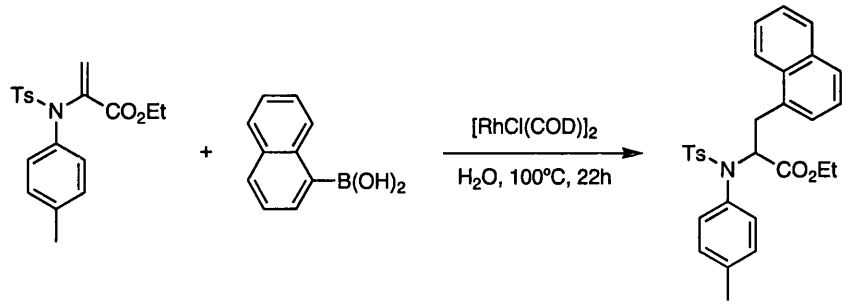
Triethylamine (31.22 ml, 224.0 mmol) was added to a cooled solution of 4-methylaniline (6.0 g, 56.0 mmol), tosyl chloride (10.14 g, 53.2 mmol) in anhydrous dichloromethane (50 mL), –5 °C, The reaction was stirred for 22 hours at room temperature, then water (50 ml) was added, and the layers separated. The aqueous layer was washed with dichloromethane (40 ml). The combined organic layers were washed with hydrochloric acid (2 M, 40 ml) and the aqueous layer further washed with dichloromethane (30 ml). The resulting organic layers were combined washed with brine (50 ml), and dried over $MgSO_4$, filtered and solvent removed *in vacuo* to leave crude product as an orange solid (12.86 g). Purification by flash chromatography (petrol:diethyl ether), and trituration with diethyl ether afforded the title compound as a colourless solid (9.94 g, 71%). R_f (petrol-ethyl acetate, 2:1) 0.12; mp 118-119 °C, lit. 118-118.7 °C (recrystallised from ethanol)[201]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.26 (3H, s), 2.37 (3H, s), 6.83 (1H, s), 6.95 (2H, d, J = 8.7), 7.02 (2H, d, J = 8.7), 7.21 (2H, d, J = 8.6), 7.65 (2H, d, J = 8.6); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 143.7, 136.1, 135.3, 133.7, 129.8, 129.6, 127.3, 122.2, 21.5, 20.8; IR (thin film) ν 3261, 2922, 2360, 1598, 1511, 1457, 1394, 1330, 1301, 1222, 1160, 1092, 1020, 911, 813, 668.

2-[(Toluene-4-sulphonyl)-*p*-tolyl-amino]-acrylic acid ethyl ester 196



To a solution of 4-methyl-*N*-*p*-tolyl-benzenesulphonamide (5.0 g, 19.1 mmol), triphenylphosphine (0.5 g, 1.91 mmol), and sodium acetate (785 mg, 9.56 mmol) in 30 mL of anhydrous toluene at 105 °C were added sequentially acetic acid (0.55 mL, 9.56 mmol) and ethylpropiolate (1.94 mL, 19.1 mmol). After 18 h, the cooled reaction mixture was directly chromatographed on silica gel (petrol:diethyl ether, 2:1) to yield 3.40 g (49%) of acrylate **196** as a dark red oil. R_f (petrol-ethyl acetate, 9:1) 0.24; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24 (3H, t, J = 7.2), 2.31 (3H, s), 2.41 (3H, s), 4.17 (2H, q, J = 7.2), 5.80 (1H, s), 6.29 (1H, s), 7.07 (2H, d, J = 8.8), 7.16 (2H, d, J = 8.8), 7.23 (2H, d, J = 8.4), 7.63 (2H, d, J = 8.4); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 164.1, 143.7, 139.0, 138.1, 136.9, 136.9, 129.8, 129.3, 128.6, 128.1, 125.6, 61.7, 21.6, 21.1, 14.0; IR (thin film) ν 2982, 2359, 1776, 1728, 1625, 1598, 1507, 1355, 1314, 1240, 1166, 1119, 1092, 1021, 957, 915, 815, 801, 731, 711, 687, 660, 579, 545; MS (FAB$^+$): m/z 360.0 (100%, MH^+).

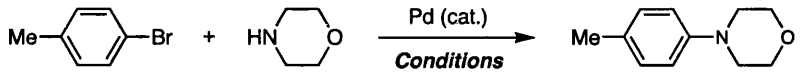
Rhodium-catalysed 1,4-addition of 1-naphthaleneboronic acid to 2-[(toluene-4-suphonyl)-*p*-tolyl-amino]-acrylic acid ethyl ester



A suspension of 2-[(toluene-4-sulphonyl)-*p*-tolyl-amino]-acrylic acid ethyl ester **196** (180 mg, 0.5 mmol), 1-naphthaleneboronic acid (172 mg, 1.0 mmol), and chloro-(1,5-cyclooctadiene)rhodium(I) dimer (12 mg, 0.025 mmol), in 3 mL of water was refluxed for 24 h under an air atmosphere. After this time ethyl acetate (10 mL) was added and the phases separated, the aqueous phase was further extracted with ethyl acetate (3 × 10 mL). The combined organics were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash chromatography on silica gel (petrol:ethyl acetate, 4:1) isolated the starting material with signals present in the ^1H NMR indicative of the desired product.

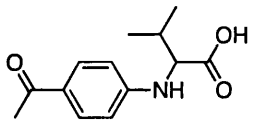
6.9 Synthesis of N-Aryl-α-Amino Acids: Palladium Catalysis

Typical procedure for the synthesis of 4-*p*-tolylmorpholine 210 *via* the palladium catalysed amination reaction



An oven dried pressure tube was cooled to room temperature under an atmosphere of nitrogen, and charged with bromotoluene (171 mg, 1.0 mmol), morpholine (105 μL, 1.2 mmol), sodium *tert*-butoxide (135 mg, 1.4 mmol), [Pd_2dba_3] (9.2 mg, 10 μmol, 2 mol % Pd), ligand (20 μmol, 2 mol %) and toluene (1 mL, 0.5 M). The tube was sealed and heated at 100 °C for 6 hours, after which time it was allowed to cool to room temperature. The resulting mixture was diluted with ethyl acetate and filtered through a celite plug. Purification by flash chromatography (petrol:ethyl acetate) afforded the title compound in 93% yield (165 mg). R_f (petrol:ethyl acetate, 4:1) 0.49; ^{1}H NMR (300 MHz) δ 2.27 (3H, s, CH_3), 3.10 (4H, t, J = 4.7, CH_2N), 3.85 (4H, t, J = 4.7, CH_2O), 6.84 (2H, d, J = 8.7, C*H*CN), 7.09 (2H, d, J = 8.7, C*H*CCH_3); ^{13}C NMR (75.5 MHz) δ 149.19 (CN), 129.70 (*C*HCCH_3), 129.56 (*C*CH_3), 116.02 (*C*HCN), 66.98 (CH_2O), 49.92 (CH_2N), 20.42 (CH_3); IR (film, cm^{-1}) ν 2976, 2956, 2853, 2829, 2748, 2695, 1971, 1894, 1612, 1577, 1515, 1452, 1379, 1364, 1327, 1312, 1297, 1259, 1237, 1168, 1118, 1064, 1048, 1031, 922, 857, 818, 755, 706, 666, 608, 530; HRMS (EI$^+$) calcd for $C_{11}H_{15}NO$ [M^+]: m/z 177.1154; found: m/z 177.1154. Data identical to those in the literature.[202]

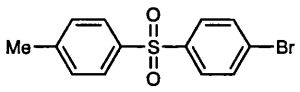
2-(4-acetylphenylamino)-3-methylbutanoic acid 213



Prepared in accordance with the literature procedure.[179]

A Schlenk tube was charged with L-Valine (469 mg, 4.0 mmol), 4-bromoacetophenone (796 mg, 4.0 mmol), potassium carbonate (829 mg, 6.0 mmol), and copper(I) iodide (76 mg, 0.4 mmol). Under a nitrogen atmosphere, dimethylformamide (4 mL) was added by syringe. The tube was sealed and heated at 90 °C for 48 hours. After being cooled to room temperature, the reaction mixture was diluted with 10 mL of ethyl acetate and 5 mL of water. Under cooling with ice/water, concentrated hydrochloric acid was added to adjust the pH to 3. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (5 × 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated to dryness under reduced pressure. Purification by flash chromatography afforded the title compound as a colourless crystalline solid (668 mg, 71% yield). Mp 141-142 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.07 (6H, t, *J* = 6.9), 2.23 (1H, dsep, *J* = 5.5, 6.9), 2.50 (3H, s), 4.01 (1H, d, *J* = 5.5), 6.61 (2H, d, *J* = 8.7), 7.82 (2H, d, *J* = 8.7); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 197.2, 177.3, 151.3, 131.1, 127.4, 112.1, 61.2, 31.3, 26.0, 19.0, 18.4; IR (film, cm^{-1}) ν 3018, 2968, 1719, 1657, 1597, 1529, 1486, 1468, 1425, 1361, 1281, 1216, 1182, 960, 826, 756, 668; Optical rotation: $[\alpha]_D^{25}$ –144° (*c*=0.09, EtOH); MS (FAB$^+$): *m/z* 236.2 (100%, MH$^+$); HRMS (FAB$^+$) calcd for $C_{13}H_{18}NO_3$ [*MH*$^+$]: *m/z* 236.1287; found: *m/z* 236.1276; Anal. calcd for $C_{13}H_{17}NO_3$: C 66.36, H 7.28, N 5.95; found: C 66.2, H 7.34, N 5.70%.

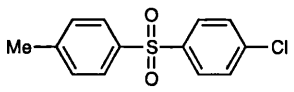
(4-bromophenyl)-*p*-tolyl sulphone 158a



Prepared in accordance with the literature procedure.[188]

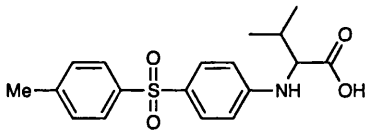
Indium triflate (0.72 g, 1.29 mmol), bromobenzene (2.70 mL, 25.7 mmol) and tosyl chloride (2.45 g, 12.85 mmol), were stirred under nitrogen and heated to 120 °C for 18 hours. The reaction mixture was cooled to room temperature and partitioned between dichloromethane and hydrochloric acid (1 M). The aqueous layer was washed with dichloromethane three times and the combined organics were washed with brine, dried over $MgSO_4$ and concentrated to yield a white crystalline solid (2.44 g ,61% yield). Mp 137 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.40 (3H, s, CH_3), 7.31 (2H, d, J = 8.4, Ar), 7,63 (2H, d, J = 8.4, Ar), 7.78 (2H, d, J = 5.6, Ar), 7.81 (2H, d, J = 5.6, Ar); ^{13}C NMR (63 MHz, $CDCl_3$) δ 132.7, 130.2, 129.2, 127.9, 22.0; MS (FAB$^+$): *m/z* 313.2 (41%, MH(^{81}Br)$^+$); *m/z* 311.0 (41%, MH(^{79}Br)$^+$).

(4-chlorophenyl)-*p*-tolyl sulphone 158b



Indium triflate (0.72 g, 1.29 mmol), chlorobenzene (3.05 mL, 30.0 mmol) and tosyl chloride (2.86 g, 15.0 mmol), were stirred under nitrogen and heated to 120 °C for 18 hours. The reaction mixture was cooled to room temperature and partitioned between dichloromethane and hydrochloric acid (1 M). The aqueous layer was washed with dichloromethane three times and the combined organics were washed with brine, dried over $MgSO_4$ and concentrated to yield a colourless crystalline solid (2.96 g, 74% yield). Mp 120 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.40 (3H, s, CH_3), 7.31 (2H, d, J = 7.8, Ar), 7,46 (2H, m, Ar), 7.80 (2H, d, J = 12.0, Ar), 7.86 (2H, m, Ar); ^{13}C NMR (63 MHz, $CDCl_3$) δ 130.2, 129.7, 129.1, 127.9, 22.0; MS (FAB$^+$): *m/z* 269.1 (38%, MH(^{37}Cl)$^+$); *m/z* 267.0 (100%, MH(^{35}Cl)$^+$).

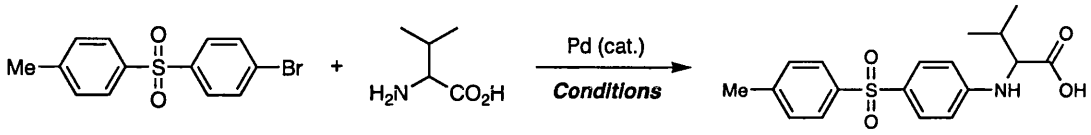
2-(4-tosylphenylamino)-3-methylbutanoic acid 214



Prepared in accordance with the literature procedure.[179]

A Schlenk tube was charged with L-Valine (59 mg, 0.5 mmol), (4-bromophenyl)-*p*-tolyl sulphone (156 mg, 0.5 mmol), potassium carbonate (104 mg, 0.75 mmol), and copper(I) iodide (9.5 mg, 0.05 mmol). Under a nitrogen atmosphere, dimethylformamide (1 mL) was added by syringe. The tube was sealed and heated at 90 °C for 48 hours. After being cooled to room temperature, the reaction mixture was diluted with 5 mL of ethyl acetate and 3 mL of water. Under cooling with ice/water, concentrated hydrochloric acid was added to adjust the pH to 3. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (5 × 5 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated to dryness under reduced pressure. Purification by flash chromatography afforded the title compound as a colourless crystalline solid (89 mg, 51% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.04 (6H, t, J = 6.5, CH_3), 2.20 (1H, m, NHC*H*), 2.38 (3H, s, ArCH_3), 3.94 (1H, d, J = 5.2, CHCO), 4.58 (1H, br s, NH), 6.61 (2H, d, J = 8.9, *Ar*CNH), 7.25 (2H, d, J = 8.1, *Ar*CCH_3), 7.71 (2H, d, J = 8.9, Ar), 7.77 (2H, d, J = 8.1, Ar); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 177.7, 151.3, 143.9, 140.2, 130.2, 130.0, 129.7, 127.5, 113.0, 61.7, 31.6, 21.9, 19.4, 18.7.

Typical procedure for the synthesis of 2-(4-tosylphenylamino)-3-methylbutanoic acid *via* the palladium catalysed amination reaction



An oven dried pressure tube was cooled to room temperature under an atmosphere of nitrogen, and charged with (4-bromophenyl)-*p*-tolyl sulphone (156 mg, 0.5 mmol), L-valine (70 mg, 0.6 mmol), sodium *tert*-butoxide (125 mg, 1.3 mmol), [Pd_2dba_3] (4.6 mg, 5 μmol, 2 mol % Pd), (rac)-BINAP (6.2 mg, 10 μmol, 2 mol %), toluene (1 mL, 0.5 M). The tube was sealed and heated at 100 °C for 6 hours, after which time it was allowed to cool to room temperature. The reaction mixture was dissolved in ethyl acetate (5 mL) and washed with hydrochloric acid (2 M, 5 mL), the layers were separated and the aqueous was washed with ethyl acetate (4 × 5 mL). The combined organics were washed with brine and dried over $MgSO_4$. Solvents were evaporated *in vacuo* to yield a mixture of starting material and products, analysis by NMR spectroscopy determined the percentile conversion.

CHAPTER SEVEN:

References

7 References

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APPENDICES:

APPENDIX 1: CRYSTAL DATA FOR LIGAND 143 AND PALLADIUM POMPLEXES 147, 149 AND 151

Full data can be found on the accompanying CD.

Table A - 1 Selected intramolecular distances (Å) and angles (°) for ligand **143** and palladium complexes **147, 149** and **151**

Compound **143**					
S(1)-O(2)	1.4370 (14)	C(6)-P(1)-C(12)	98.08(8)		
S(1)-O(1)	1.4442 (14)	C(13)-P(1)-C(6)	105.34(9)		
P(1)-C(13)	1.8210 (19)	C(13)-P(1)-C(12)	102.47(8)		
P(1)-C(6)	1.832(2)				
P(1)-C(12)	1.8344(18)				
Compound **147**					
Pd(1)-P(1)	2.2454(8)	N(1)-Pd(1)-P(1)	173.50(9)	C(41)-P(1)-Pd(1)	109.99(10)
Pd(1)-N(1)	2.132(3)	C(11)-Pd(1)-Cl(1)	174.07(9)	C(21)-P(1)-Pd(1)	124.02(10)
Pd(1)-Cl(1)	2.3872(8)	C(11)-Pd(1)-N(1)	81.28(12)	C(31)-P(1)-Pd(1)	117.42(10)
Pd(1)-C(11)	2.024(3)	N(1)-Pd(1)-Cl(1)	92.81(8)	C(21)-P(1)-C(31)	99.39(14)
Pd(1)-O(2)	3.768(2)	P(1)-Pd(1)-Cl(1)	86.55(3)	C(41)-P(1)-C(21)	100.18(13)
S(1)-O(1)	1.436(2)	C(11)-Pd(1)-P(1)	99.38(9)	C(41)-P(1)-C(31)	102.72(14)
S(1)-O(2)	1.434(2)	P(1)-Pd(1)-O(2)	60.52(4)		
Pd(2)-P(2)	2.2650(7)	N(2)-Pd(2)-P(2)	177.22(7)	C(71)-P(2)-Pd(2)	122.28(10)
Pd(2)-N(2)	2.135(2)	C(81)-Pd(2)-Cl(2)	173.08(8)	C(51)-P(2)-Pd(2)	111.97(9)
Pd(2)-Cl(2)	2.3856(7)	C(81)-Pd(2)-N(2)	82.03(11)	C(61)-P(1)-Pd(2)	123.59(9)
Pd(2)-C(81)	2.020(3)	N(2)-Pd(2)-Cl(2)	91.47(7)	C(61)-P(2)-C(51)	98.56(13)
Pd(2)-O(4)	3.407(2)	P(2)-Pd(2)-Cl(2)	85.76(3)	C(71)-P(1)-C(51)	104.11(14)
S(2)-O(3)	1.439(2)	C(81)-Pd(2)-P(2)	100.74(9)	C(71)-P(1)-C(61)	103.99(14)
S(2)-O(4)	1.440(2)	P(2)-Pd(2)-O(4)	67.04(4)		
Compound **149**					
Pd(1)-P(1)	2.2504(4)	N(1)-Pd(1)-P(1)	167.79(5)	C(11)-P(1)-Pd(1)	120.46(6)
Pd(1)-N(1)	2.1408(15)	C(41)-Pd(1)-O(4)	173.97(6)	C(31)-P(1)-Pd(1)	114.28(5)
Pd(1)-O(4)	2.2077(12)	C(41)-Pd(1)-N(1)	81.94(7)	C(21)-P(1)-Pd(1)	110.72(5)
Pd(1)-C(41)	1.9810(17)	N(1)-Pd(1)-O(4)	93.02(5)	C(21)-P(1)-C(31)	100.64(8)
Pd(1)-O(1)	3.1200(14)	P(1)-Pd(1)-O(4)	92.52(4)	C(11)-P(1)-C(31)	105.17(7)
S(1)-O(1)	1.4439(13)	C(41)-Pd(1)-P(1)	93.06(5)	C(11)-P(1)-C(21)	103.26(8)
S(1)-O(2)	1.4397(14)	P(1)-Pd(1)-O(1)	73.06(3)		
Compound **151**					
Pd(1)-P(1)	2.2462(4)	N(1)-Pd(1)-P(1)	165.19(4)	C(10)-P(1)-Pd(1)	120.20(5)
Pd(1)-N(1)	2.1352(14)	C(1)-Pd(1)-O(3)	176.47(6)	C(22)-P(1)-Pd(1)	111.33(5)
Pd(1)-O(3)	2.2031(13)	C(1)-Pd(1)-N(1)	81.89(6)	C(16)-P(1)-Pd(1)	110.61(5)
Pd(1)-C(1)	1.9793(16)	N(1)-Pd(1)-O(3)	94.98(5)	C(16)-P(1)-C(22)	99.53(7)
Pd(1)-O(1)	2.9454(12)	P(1)-Pd(1)-O(3)	91.91(4)	C(10)-P(1)-C(22)	109.58(7)
S(1)-O(1)	1.4402(13)	C(1)-Pd(1)-P(1)	91.51(5)	C(10)-P(1)-C(16)	103.34(7)
S(1)-O(2)	1.4430(12)	P(1)-Pd(1)-O(1)	78.04(3)		

Estimated standard deviations in the least significant figure are given in parentheses

Table A - 2 Crystal data and structure refinement for ligand **143**

Identification code	h01cgf1
Empirical formula	$C_{18}H_{13}O_2PS$
Formula weight	324.31
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	P-1
Unit cell dimensions	a = 7.9730(2)Å α = 100.879(1)°
	b = 8.1510(2)Å β = 93.402(2)°
	c = 13.2550(6)Å γ = 113.676(2)°
Volume	765.94(4) $Å^3$
Z	2
Density (calculated)	1.406 Mg/m^3
Absorption coefficient	0.319 mm^{-1}
F(000)	336
Crystal size	0.50 x 0.40 x 0.20 mm
Theta range for data collection	3.44 to 27.48 °.
Index ranges	-10<=h<=10; -10<=k<=10; -17<=l<=17
Reflections collected	10933
Independent reflections	3472 [R(int) = 0.0349]
Reflections observed (>2σ)	2857
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3472 / 0 / 200
Goodness-of-fit on F^2	1.035
Final R indices [I>2σ(I)]	R_1 = 0.0407 wR_2 = 0.1061
R indices (all data)	R_1 = 0.0541 wR_2 = 0.1132
Largest diff. peak and hole	0.825 and -0.456 $e.Å^{-3}$

Table A - 3 Crystal data and structure refinement for complex **147**

Identification code	h01cgf3
Empirical formula	$C_{27}H_{25}ClNO_2PPdS$
Formula weight	600.36
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	P-1
Unit cell dimensions	a = 10.42500(10)Å α = 79.8910(5)°
	b = 13.7540(2)Å β = 88.0700(5)°
	c = 17.6450(3)Å γ = 81.0550(8)°
Volume	2460.41(6) $Å^3$
Z	4
Density (calculated)	1.621 Mg/m^3
Absorption coefficient	1.039 mm^{-1}
F(000)	1216
Crystal size	0.15 x 0.15 x 0.15 mm
Theta range for data collection	3.58 to 27.10 °.
Index ranges	-13<=h<=13; -17<=k<=17; -22<=l<=22
Reflections collected	40344
Independent reflections	10805 [R(int) = 0.0408]
Reflections observed (>2σ)	9050
Data Completeness	0.994
Absorption correction	Multiscan
Max. and min. transmission	0.8597 and 0.8597
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	10805 / 0 / 618
Goodness-of-fit on F^2	0.790
Final R indices [I>2σ(I)]	R_1 = 0.0334 wR_2 = 0.0890
R indices (all data)	R_1 = 0.0454 wR_2 = 0.0986
Largest diff. peak and hole	0.831 and -1.113 $e.Å^{-3}$

Table A - 4 Crystal data and structure refinement for complex **149**

Identification code	k01cgf1
Empirical formula	$C_{28}H_{25}F_3NO_5PPdS_2$
Formula weight	713.98
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/n$
Unit cell dimensions	a = 9.45900(10)Å α = 90°
	b = 12.11100(10)Å β = 100.0270(3)°
	c = 25.6990(2)Å γ = 90°
Volume	2899.06(4) $Å^3$
Z	4
Density (calculated)	1.636 Mg/m^3
Absorption coefficient	0.898 mm^{-1}
F(000)	1440
Crystal size	0.20 x 0.18 x 0.18 mm
Theta range for data collection	3.73 to 30.03°
Index ranges	-13<=h<=13; -17<=k<=17; -36<=l<=36
Reflections collected	56679
Independent reflections	8465 [R(int) = 0.0367]
Reflections observed (>2σ)	7497
Data Completeness	0.998
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.46 and 0.43
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	8465 / 0 / 373
Goodness-of-fit on F^2	0.577
Final R indices [I>2σ(I)]	R_1 = 0.0256 wR_2 = 0.0769
R indices (all data)	R_1 = 0.0310 wR_2 = 0.0857
Largest diff. peak and hole	0.473 and -0.799 $eÅ^{-3}$

Table A - 5 Crystal data and structure refinement for complex **151**

Identification code	h01cgf4
Empirical formula	$C_{27}H_{27}F_6NO_3PPdSSb$
Formula weight	818.68
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/n$
Unit cell dimensions	a = 13.7950(1)Å α = 90°
	b = 14.2050(1)Å β = 104.11°
	c = 15.4340(2)Å γ = 90°
Volume	2933.19(5) $Å^3$
Z	4
Density (calculated)	1.854 Mg/m^3
Absorption coefficient	1.729 mm^{-1}
F(000)	1608
Crystal size	0.30 x 0.30 x 0.08 mm
Theta range for data collection	3.08 to 33.14°.
Index ranges	-21<=h<=19; -21<=k<=21; -23<=l<=23
Reflections collected	59819
Independent reflections	11173 [R(int) = 0.0399]
Reflections observed (>2σ)	9319
Data Completeness	0.998
Absorption correction	Numerical
Max. and min. transmission	0.86 and 0.62
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	11173 / 2 / 381
Goodness-of-fit on F^2	1.025
Final R indices [I>2σ(I)]	R_1 = 0.0252 wR_2 = 0.0580
R indices (all data)	R_1 = 0.0359 wR_2 = 0.0617
Largest diff. peak and hole	0.740 and -0.879 $eÅ^{-3}$

APPENDIX 2: CRYSTAL DATA FOR PALLADIUM COMPLEXES 152 AND 153

Full data can be found on the accompanying CD.

Table A - 6 Selected intramolecular distances (Å) and angles (°) for palladium complexes **152** and **153**

Compound **152**					
Pd(1)-P(1)	2.2456(4)	N(1)-Pd(1)-P(1)	172.58(4)	P(1)-Pd(1)-O(2)	68.34(3)
Pd(1)-N(1)	2.1279(14)	C(1)-Pd(1)-Cl(1)	165.73(5)	C(22)-P(1)-Pd(1)	116.67(5)
Pd(1)-Cl(1)	2.4233(4)	C(1)-Pd(1)-N(1)	82.62(6)	S(1)-O(2)-Pd(1)	136.93(7)
Pd(1)-C(1)	2.0086(17)	N(1)-Pd(1)-Cl(1)	91.75(4)	O(2)-S(1)-C(27)	107.86(7)
Pd(1)-O(2)	2.9399(12)	P(1)-Pd(1)-Cl(1)	91.914(15)	C(22)-C(27)-S(1)	124.05(12)
S(1)-O(1)	1.4380(13)	C(1)-Pd(1)-P(1)	95.23(5)	C(27)-C(22)-P(1)	124.41(12)
S(1)-O(2)	1.4379(13)				
Compound **153**					
Pd(1)-P(1)	2.2486(4)	N(1)-Pd(1)-P(1)	174.88(4)	C(34)-P(1)-Pd(1)	113.55(5)
Pd(1)-N(1)	2.1191(13)	C(1)-Pd(1)-O(1)	166.77(6)	S(1)-O(1)-Pd(1)	127.68(7)
Pd(1)-O(1)	2.1508(11)	C(1)-Pd(1)-N(1)	83.22(6)	O(1)-S(1)-C(39)	107.16(7)
Pd(1)-C(1)	1.9913(15)	N(1)-Pd(1)-O(1)	93.29(5)	C(34)-C(39)-S(1)	125.06(12)
S(1)-O(1)	1.4711(12)	P(1)-Pd(1)-O(1)	82.14(3)	C(39)-C(34)-P(1)	126.22(12)
S(1)-O(2)	1.4307(12)	C(1)-Pd(1)-P(1)	100.71(5)		

Estimated standard deviations in the least significant figure are given in parentheses

Table A - 7 Crystal data and structure refinement for complex **152**

Identification code	k01cgf5
Empirical formula	$C_{41.25}$ H_{50} Cl_3 N_2 O_2 P Pd S
Formula weight	881.61
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	P-1
Unit cell dimensions	a = 10.62000(10)Å α = 108.52°
	b = 15.32700(10)Å β = 100.29°
	c = 15.39800(10)Å γ = 108.9620(10)°
Volume	2133.66(3) $Å^3$
Z	2
Density (calculated)	1.372 Mg/m^3
Absorption coefficient	0.745 mm^{-1}
F(000)	911
Crystal size	0.37 x 0.25 x 0.25 mm
Theta range for data collection	3.53 to 30.09°
Index ranges	-14<=h<=13; -20<=k<=21; -21<=l<=21
Reflections collected	43431
Independent reflections	12423 [R(int) = 0.0329]
Reflections observed (>2σ)	10845
Data Completeness	0.991
Max. and min. transmission	0.8357 and 0.7701
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	12423 / 0 / 476
Goodness-of-fit on F^2	1.035
Final R indices [I>2σ(I)]	R_1 = 0.0310 wR_2 = 0.0837
R indices (all data)	R_1 = 0.0381 wR_2 = 0.0872
Largest diff. peak and hole	0.790 and -0.689 e.$Å^{-3}$

Table A - 8 Crystal data and structure refinement for complex **153**

Identification code	k02cgf2
Empirical formula	C_{39} H_{48} F_6 N_2 O_2 P Pd S Sb
Formula weight	981.97
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/n$
Unit cell dimensions	a = 18.4920(2)Å α = 90°
	b = 12.2630(1)Å β = 102.40°
	c = 18.5860(2)Å γ = 90°
Volume	4116.44(7) $Å^3$
Z	4
Density (calculated)	1.584 Mg/m^3
Absorption coefficient	1.245 mm^{-1}
F(000)	1976
Crystal size	0.30 x 0.30 x 0.13 mm
Theta range for data collection	3.61 to 30.04°
Index ranges	-26<=h<=25; -17<=k<=17; -26<=l<=26
Reflections collected	80179
Independent reflections	12008 [R(int) = 0.0425]
Reflections observed (>2σ)	10667
Data Completeness	0.995
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.86 and 0.78
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	12008 / 0 / 518
Goodness-of-fit on F^2	1.055
Final R indices [I>2σ(I)]	R_1 = 0.0244 wR_2 = 0.0609
R indices (all data)	R_1 = 0.0305 wR_2 = 0.0646
Largest diff. peak and hole	0.884 and -0.803 $eÅ^{-3}$

APPENDIX 3: CRYSTAL DATA FOR RHODIUM COMPLEX 155

Full data can be found on the accompanying CD.

Table A - 9 Selected intramolecular distances (Å) and angles (°) for rhodium complex **155**

Rh(1) – P(1)	2.2691(13)	C(21)-P(1)-Rh(1)	110.07(16)
Rh(1) – O(1)	2.131(3)	O(1)-Rh(1)-P(1)	81.08(10)
S(1) – O(1)	1.468(4)	S(1)-O(1)-Rh(1)	122.4(2)
S(1) – O(2)	1.424(4)	O(1)-S(1)-C(26)	107.8(2)
		C(21)-C(26)-S(1)	125.4(4)
		C(26)-C(21)-P(1)	124.3(4)

Estimated standard deviations in the least significant figure are given in parentheses

Table A - 10 Crystal data and structure refinement for complex **155**

Identification code	h02cgf3
Empirical formula	C_{38} H_{48} F_6 N O_2 P Rh S Sb
Formula weight	952.46
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	C2/c
Unit cell dimensions	a = 26.9170(3)Å α = 90°
	b = 10.7020(1)Å β = 112.1451(4)°
	c = 29.9170(4)Å γ = 90°
Volume	7982.33(16) $Å^3$
Z	8
Density (calculated)	1.585 Mg/m^3
Absorption coefficient	1.244 mm^{-1}
F(000)	3840
Crystal size	0.33 x 0.20 x 0.08 mm
Theta range for data collection	3.81 to 27.50°
Index ranges	-34<=h<=34; -13<=k<=13; -38<=l<=38
Reflections collected	53953
Independent reflections	9124 [R(int) = 0.1005]
Reflections observed (>2σ)	6096
Data Completeness	0.995
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.91 and 0.45
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	9124 / 26 / 461
Goodness-of-fit on F^2	1.023
Final R indices [I>2σ(I)]	R_1 = 0.0657 wR_2 = 0.1521
R indices (all data)	R_1 = 0.1027 wR_2 = 0.1728
Largest diff. peak and hole	0.869 and -1.071 $eÅ^{-3}$

APPENDIX 4: CRYSTAL DATA FOR LIGAND 183B

Full data can be found on the accompanying CD.

Table A - 11 Selected intramolecular distances (Å) and angles (°) for ligand **183b**

P-N	1.637(5)	N-P-O(3)	95.2(2)
P-O(3)	1.672(5)	N-P-O(4)	110.6(3)
P-O(4)	1.690(5)	O(3)-P-O(4)	96.7(2)
S(1)-C(21)	1.847(8)	C(1)-O(3)-P	117.6(4)
S(2)-C(24)	1.850(11)	C(11)-O(4)-P	124.5(4)
N-C(23)	1.459(9)	C(23)-N-C(22)	114.0(5)
N-C(22)	1.462(8)	C(23)-N-P	126.4(4)
O(3)-C(1)	1.387(7)	C(22)-N-P	118.4(4)
O(4)-C(11)	1.389(8)	(C(1)-C(10))-(C(20)-C(11))	54.4

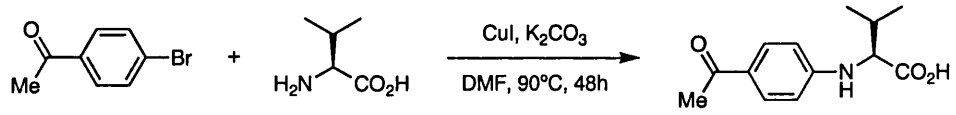
Estimated standard deviations in the least significant figure are given in parentheses

Table A - 12 Crystal data and structure refinement for lignad **183b**

Identification code	K03cgf1
Empirical formula	$C_{24}\ H_{17}\ F_6\ N\ O_{6.5}\ P\ S_2$
Formula weight	632.48
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	I222 (no.23)
Unit cell dimensions	a = 11.2220(10)Å α = 90°
	b = 14.5210(5)Å β = 90°
	c = 36.7920(4)Å γ = 90°
Volume	5995.4(6) $Å^3$
Z	8
Density (calculated)	1.401 Mg/m^3
Absorption coefficient	0.307 mm^{-1}
F(000)	2568
Crystal size	0.38 x 0.38 x 0.10 mm
Theta range for data collection	3.73 to 27.08°
Index ranges	-13<=h<=13; -18<=k<=17; -42<=l<=45
Reflections collected	29203
Independent reflections	6066 [R(int) = 0.1609]
Absolute structure parameter	0.01(16)
Data Completeness	0.927
Extinction coefficient	0.0038(5)
Max. and min. transmission	0.9700 and 0.8923
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	6066 / 0 / 368
Goodness-of-fit on F^2	1.093
Final R indices [I>2σ(I)]	R_1 = 0.0928 wR_2 = 0.2056
R indices (all data)	R_1 = 0.1134 wR_2 = 0.2219
Largest diff. peak and hole	0.506 and -0.474 $eÅ^{-3}$

APPENDIX 5

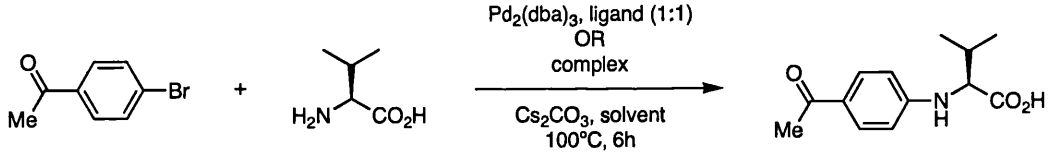
In collaboration with Johnson-Matthey Plc parallel optimisation experiments were performed using a Radley's 12-position carousel with reaction efficiency assessed by HPLC analysis. The reaction of 4-bromoacetophenone with L-valine was chosen as the standard reaction. The desired coupled product was prepared *via* the procedure reported by Ma *et al.* (Scheme A - 1).[1]



Scheme A - 1

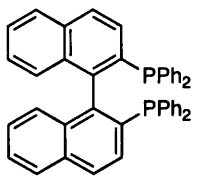
Five solvents were tested, with eleven different ligands or preformed palladium complexes; all other variables were kept constant (Scheme A - 2, Graph A - 1). HPLC analysis was performed using a Hyperid ODS (5μ, 100×4.6 mm) reverse phase column with a gradient elution over 7 miutes. Spectra were recorded at 330nm, corresponding to the peak maximum of the product. Whilst calibration of the intensities of product and starting material was not performed, the results obtained highlighted the production of the desired product supplying *hits* for further analysis.

[1] Ma, D. W.; Zhang, Y. D.; Yao, J. C.; Wu, S. H.; Tao, F. G. *J. Am. Chem. Soc.* **1998**, *120*, 12459-12467.



Solvent = toluene
trifluorotoluene
dioxane
trifluoroethanol
DMF

Ligands/
Complexes:



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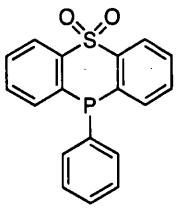

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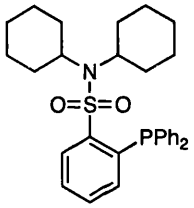

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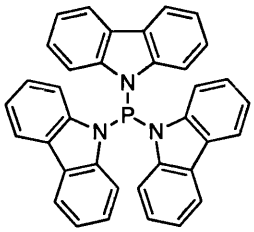

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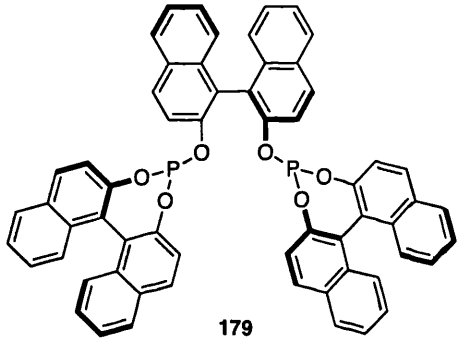

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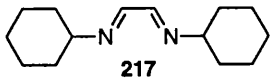

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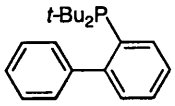
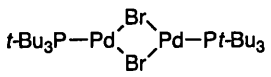


125b



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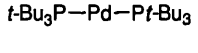

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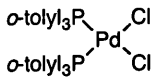

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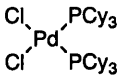

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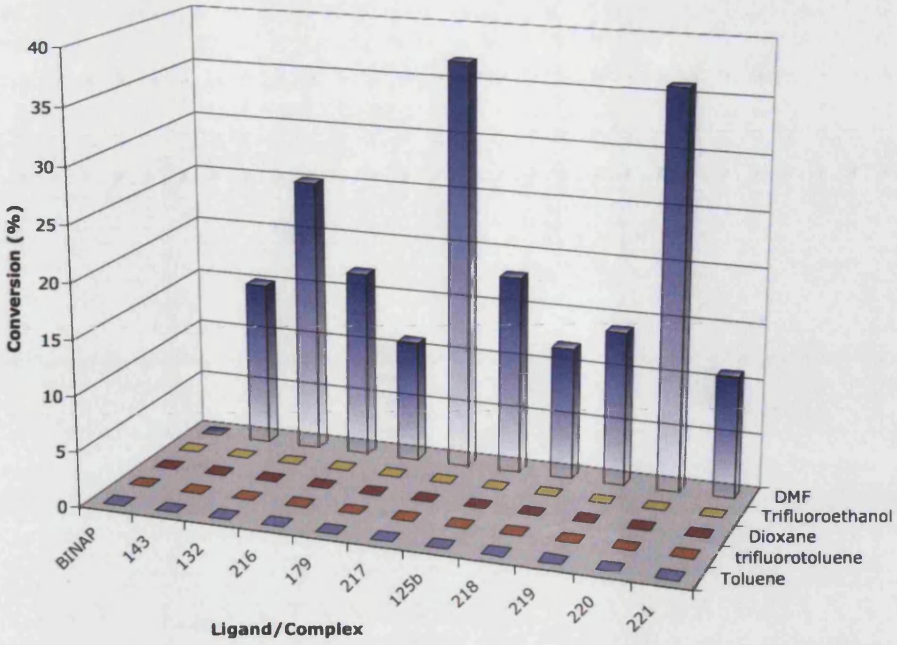
Scheme A - 2



Graph A - 1 *N*-Arylation of L-valine

Disappointingly traces of product were detected, solely when dimethylformamide was solvent. (3*E*)-*N*-((*E*)-2-(cyclohexylimino)ethylidene)cyclohexanamine **217** and complex **220** produced the most promising results. However, further testing with these conditions gave no appreciable conversion when the reactions were performed independently. The low conversions observed were attributed to the use of the weak base caesium carbonate, as such further coupling reactions utilised the stronger sodium or potassium *tert*-butoxide as base.